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BRITISH MEDICAL JOURNAL

LONDON SATURDAY JANUARY 30 1954

THE VALUE OF PHYSIOLOGY IN MEDICINE*

BY

GEORGE GRAHAM, M.D., F.R.C.P.

Consulting Physician to St. Bartholomew's Hospital

First of all I wish to thank you for the honour you have done me in inviting me to deliver the two hundred and thirty-fourth Harveian Oration; secondly, to commemorate the memory of William Harvey, and all other benefactors of the College. Although I had learnt a little about Harvey in my physiology days, I did not really appreciate the magnitude of his achievement until the tercentenary of the publication of his great work, *De Motu Cordis*, which was celebrated in this College in 1928. I was especially impressed by the cinematograph film prepared by Sir Thomas Lewis and Sir Henry Dale, which demonstrated most clearly the arguments and experiments which he used to prove that the blood circulated through the heart. The film is now shown to all physiology students, but it is unfortunate that many of the men and women who qualified before 1928 have not had an opportunity of seeing it, and of appreciating to the full the value of Harvey's work. I should have liked to show the film this afternoon, but it would have taken too long. I hope, however, that all the members of the staffs of teaching hospitals, and not only the physicians, will take the opportunity of seeing it when it is demonstrated to their students, and so realize the difficulties which Harvey overcame. He has been called the first of the physiologists, and it is for this reason that I have chosen as a title "The Value of Physiology in Medicine."

Although the science of physiology progressed slowly throughout the centuries, there was often a tendency to decry its value. This is well shown by the experience of Sir Henry Dale, when a little more than 50 years ago he clerked for that very able clinician, Dr. Samuel Gee. He was told, "When you enter my wards your first duty is to forget all your physiology. Physiology is an experimental science—and a very good thing, no doubt, in its proper place. Medicine is not a science but an empirical art, and it is as such that you may learn something of it here" (Dale, 1950). I do not know how much Dale learnt of the "empirical art," but he has carried out himself, and has directed, much research work which has been of very great value in the whole field of medicine. He has therefore greatly helped to advance the day which Gee indeed foresaw, that "some day medicine, too, might become an experimental science." When I came down from Cambridge 49 years ago nothing so foolish was said to me, but no one seemed to pay any attention to physiology. Thus when I was a surgical dresser I was astonished to hear Sir Anthony Bowlby, an able surgeon, call for very hot saline in the course of an operation, and I was told that this was done to stop haemorrhage. This seemed most extraordinary, as the heat would, I thought, cause dilatation of the blood vessels and capillaries, and increase the bleeding, but the house-surgeon assured me that it did stop haemorrhage. I was too frightened to ask Bowlby for the explanation, which I think he might have known.

*The Harveian Oration delivered at the Royal College of Physicians of London on October 16, 1953.

Advances in Physiology

The advances in physiology have been made not only by those who work in the physiological laboratories but also by the whole army of clinicians, chemists, biochemists, biologists, physicists, anatomists, pharmacologists, and pathologists who have contributed their experiences. The final building up of the subject must, I think, be done by the physiologists and biochemists, who test out the evidence provided by their colleagues and finally assess the value of the work.

Some clinicians have, in the past, spoken contemptuously of the value of physiology in medicine and expressed a disbelief in results obtained from a "pithed" frog. The frog has been most useful to mankind; it is cheap to buy and the brain is easily destroyed, so that the student can do his experiments without causing any pain. Many important studies have been made on its heart, and it was of value in the study of nervous reflexes, but has now been displaced by Sherrington's decerebrate cats. But it is of importance to repeat the work on different animals, for they often differ considerably. Thus the great advance which has taken place in our knowledge of scurvy was made possible by the guinea-pig. This is the only animal besides man which is unable to synthesize ascorbic acid, and develops scurvy, which can be studied, under controlled conditions, at all stages of the disease. In man, scurvy is nowadays rarely seen and it is difficult to carry out controlled experiments. But the work of Crandon *et al.* (1940) is of importance because, while Crandon was doing his full work as a surgeon, he abstained from eating anything known to contain ascorbic acid. After 116 days he had slight symptoms of scurvy, and a surgical wound on the 182nd day did not heal. Again, the first investigations on anaphylactic shock were made on guinea-pigs, which develop bronchial constriction, whereas a dog develops congestion of the liver from spasm of the hepatic veins, and in the rabbit the arterioles are constricted.

The dog has been invaluable in the study of diabetes mellitus. It was used by von Mering and Minkowski

(1890) when they removed the whole of the pancreas to study fat absorption and found that the puppy developed diabetes mellitus, and much useful information has been gained by experiments on the depancreatized dog. Young (1937) also used the dog in order to produce diabetes by injections of extracts of the anterior pituitary gland, and so destroy the islands of Langerhans. The rat, on the other hand, does not develop diabetes, no matter how much extract of the anterior pituitary is injected, and the islands of Langerhans seem larger than usual (Marks and Young, 1939).

Anaesthesia

Anaesthesia, so valuable in the treatment of patients, sometimes makes the clinical observations most misleading. Thus it is known, as a result of *x*-ray films and opaque meals, that the stomach of man in the erect posture has a J shape. But even after this had been fully established, more than 40 years ago, some surgeons refused to accept the proposition, saying that they had never seen it at operations, or in the post-mortem room. This was understandable in the operating theatre, because under the anaesthetic all the muscles are relaxed, and, if they are not, the anaesthetist is blamed. In the post-mortem room this is nearly always the case, but every now and then the stomach is found firmly contracted and of the J shape. After I knew about the shape of the stomach I was lucky enough to see it myself four times in the five years or so that I performed post-mortem examinations, the cases varying from that of a child to that of a woman who had died with her stomach full of blood from a leaking aneurysm. The stomach in this case was enormous and extended into the pelvis, and the muscles were still firmly contracted. Two specimens are now in the anatomical museum at St. Bartholomew's Hospital, but I regret to say that at first they were mounted with the long axis in the transverse instead of in the vertical position. Many others must have seen similar specimens throughout the ages, but the evidence was neglected until *x*-ray films proved the point.

In experiments on animals a doubt always exists about whether the anaesthetic has affected the results. Pituitrin was thought to be a diuretic since it caused a diuresis in the anaesthetized animal, but if an anaesthetic was not given the flow of urine decreased, and this action is of great value in the treatment of diabetes insipidus. Again, the English workers were unable to show that stimulation of the vagus caused a secretion of the juice because of the anaesthetic. Heidenhain and others in Germany also failed because they did not use any anaesthetic, and the pain prevented the secretion. Pavlov succeeded in 1895 because he isolated the vagus nerve in the neck and made an exterior pouch of the stomach under an anaesthetic. When the dog had completely recovered he stimulated the peripheral end of the nerve painlessly and observed the flow of gastric juice. Histamine, again, will kill a cat with "shock" if an ether anaesthetic is given, while the unanaesthetized cat is quite unaffected.

Animals as Test Subjects

The difference between animals, again, is of very great value and certain species will take certain diseases. Thus, the distemper of dogs also affects ferrets, and this enabled Laidlaw and his co-workers to prepare the vaccine which protects dogs from the disease. The ferret is the only animal which develops influenza when injected intranasally, though the mouse can be infected through intrapulmonary injections. Among the diseases which cannot be communicated to any animal are the common cold and rheumatic fever and infective hepatitis, and it is to be hoped that some animal will soon be found which will take these diseases, so that they may be studied more easily. Another instance is the variety of animals used for determining whether a woman is pregnant. Thus an immature female mouse (Aschheim–Zondek test), an immature female rabbit (Friedman test), a female frog (*Xenopus*), and an adult male toad (*Bufo avenarum*) are used, and the results in these four different species are said to be equally reliable. The early tests on the potency of insulin were made on the rabbit, the veins on the ear being most useful for collecting blood, but the mouse and the guinea-pig are also used for this purpose. Harvey studied the hearts of mammals, birds, snakes, fishes, and even shrimps, and insects like wasps. It is not easy to time the contraction of the auricle and ventricle by the eye in small animals, but he found it easy to confirm his impressions by watching contractions of the long heart of the adder and of the dying heart of the tortoise. These illustrations suffice to show that results which appear of value in one species must be tested on other animals, and the final experiments must be made on man himself if possible. In the physiology laboratories a good many observations are now confirmed on the students themselves, though those which involve danger cannot, of course, be performed.

Clinicians often differ very much over which hypothesis is the right one, and physiology in its wide sense is often able eventually to settle which school of thought is right. An instance of this is the treatment of rickets. One school stated that cod-liver oil was of great benefit, whereas another school asserted with equal conviction that treatment with olive oil gave results which were just as good. Mellanby's work on puppies showed that vitamin D cured rickets, and that olive oil contained none whereas cod-liver oil did, and that, if given in sufficient amounts and not diluted with malt and iron to one-quarter of its value, would cure rickets, and thus settled this controversy. The physiology which I visualize is a living and growing subject, and the principles which govern it are, I believe, of great value in the theory and treatment of medicine.

Coagulation Time

I said earlier on that as a young student I had not understood why very hot saline was used to stop oozing haemorrhage. I did not learn the explanation until nearly 20 years later when I was estimating the coagulation time of a patient with haemophilia by Dale and Laidlaw's (1911) shot method. They chose to work at a temperature of 37° C. because the coagulation time was least affected by slight alterations of temperature, and Macfarlane (1948) confirmed this.

The great shortening of the coagulation time at temperatures between 40 and 45° C. (Fig. 1) explains why the bleeding stops, although there is an increased blood supply as a result of the heat. I have asked several surgeons, and they tell me that it works

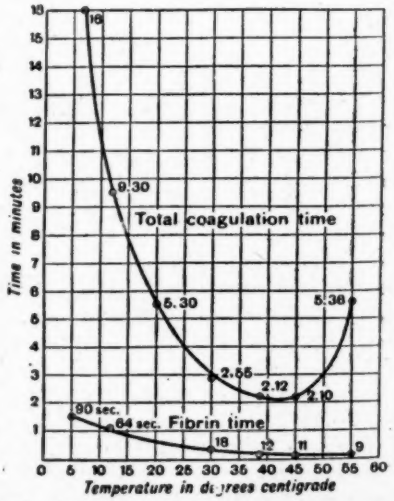

FIG. 1.—Effect of temperature upon coagulation time of normal blood.

but that they did not know the explanation. This had been given by Lister (1863) in an interesting paper on the coagulation of the blood, when he said, "It has long been known that blood coagulates more rapidly at a high temperature than at a low temperature, and that a little above freezing-point remains entirely fluid." I suppose the use of very hot saline dates from very early days, but it is peculiar that the simple physiological explanation should have been forgotten by many people. The temperature of saline used in the operating theatre is 49° C. and that of the very hot saline is about 55° C., but it is unlikely that the tissues from which the bleeding is coming reach this temperature, since at this point the coagulation time has begun to increase again. Haemophilic blood obeys the same law, and Macfarlane has observed the coagulation time at different temperatures (Fig. 2). I doubt, however, whether the shortening of the coagulation time to 12 minutes in this patient at a temperature of 55° C. would be enough to counteract the increased flow of blood.

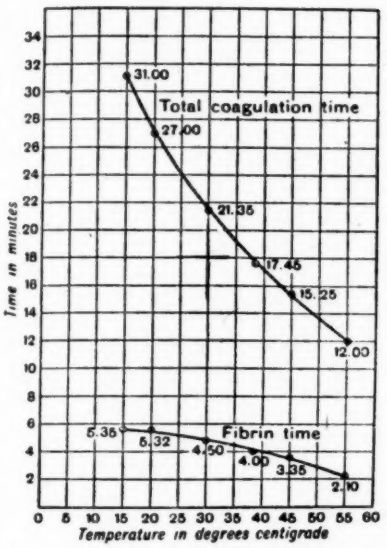

FIG. 2.—Effect of temperature upon coagulation time of haemophilic blood.

Changes in Electrolytes after Operation

There are so many diseases in which physiology is of the greatest importance that it was difficult to choose what to talk about. I finally decided to discuss the changes which take place in the water and electrolytes of the body after severe operations. A proper understanding of these has greatly improved the treatment of patients. The co-operation of the surgeon and the physician with the physiologist, biochemist, pathologist, and others in the study of disease is necessary both to advance knowledge and to apply it to the treatment of the patient. Unless this co-operation exists, practice lags far behind theory. The first advances in our knowledge were made by Sydney Ringer, Professor of Medicine to University College Hospital, 71 years ago, and were at first neglected by the clinicians. In the past ten years great advances have been made in our knowledge of electrolytes in medicine, which call for the closest co-operation of all concerned with the treatment of patients. These are well described by Gamble (1947), Darrow and Pratt (1950), and many others.

Ringer (1880–2) found that a frog's heart would beat for some hours in a solution of 0.65% NaCl—which is isotonic for the frog—as made up by his laboratory's assistant. But when the assistant fell ill, and Ringer made up his own solution with distilled water, the heart very soon ceased to beat. When the assistant recovered, and made up the solution, the heart once more continued to beat. Ringer then found that the assistant, being lazy, had not bothered to use distilled water but had used tap-water instead. This contains calcium and potassium, and Ringer (1883–4) proceeded to determine the ideal conditions for enabling the heart to beat. If calcium chloride was added to 0.65% saline, in the proportion of 1 in 19,500, a heart which had just stopped beating started again. The diastole, however, grew shorter and shorter and the heart eventually stopped in systole. If potassium chloride was added to 0.65% saline in a proportion of 1 in 10,000 instead of calcium chloride, a heart which had just stopped beating in isotonic saline started again, but this time the diastole was lengthened and the heart eventually stopped in diastole. Ringer made numerous trials, and found that both potassium and calcium were necessary, and that the best results were obtained when they were present in the same concentration as in frog's plasma (Table I). If too much potassium was added so that the heart tended to stop in diastole, the addition of extra calcium prevented the poisonous action, so that poisonous doses of both potassium and calcium might be present without affecting the heart at all (Ringer, 1884–5). I do not think many intravenous injections were made in those days, as surgical operations were nothing like so numerous or severe as they have now become.

TABLE I

	Ringer's Solution for Frogs	Ringer–Locke Solution for Man
NaCl	0·65 g.	0·9 g.
KCl	0·014 ,,	0·042 ,,
$CaCl_2$	0·012 ,,	0·024 ,,
$NaHCO_3$	0·02 ,,	0·05 ,,
NaH_2PO_4	0·001 ,,	—
Glucose	0·2 ,,	0·1 ,,
H_2O	to 100 ml.	to 100 ml.

When I came to hospital in 1905, saline, if thought necessary, was usually given subcutaneously. Many students, fresh from their physiology, must have asked, as I did, why Ringer's solution was not used, only to be told by a house-surgeon that the potassium and calcium were not necessary. I think that this was correct then, as it was rare indeed for more than 1 pint (570 ml.) of isotonic saline to be given intravenously, and it was assumed, if it was thought about at all, that the reserves of calcium in the bones and potassium in the cells would supply the necessary amounts. During the past 48 years, however, operations have increased enormously in number and magnitude. Many operations on the stomach, oesophagus, and intestines prevent any feeding by mouth for several days, and also involve evacuating the stomach or intestines by suction to prevent dilatation of these organs. Under these circumstances the amount of fluid given intravenously has been as much as 3,000–3,500 ml. a day for many days. This was sometimes isotonic saline, so that 27 g. or more of sodium chloride might be given in the day; sometimes two-thirds or one-third isotonic, so that 18 or 9 g. of sodium chloride might be given together with glucose in 5 or 10% concentration, the patient receiving as much as 150–300 g. of glucose daily.

The syndrome which results from long-continued intravenous injections of sodium chloride was first described by Whipple (1923) under the name pancreatic asthenia. He had observed asthenia, amnesia, nausea, vomiting, tendency to bleed, ptyalism, abnormal stools, epigastric pain and tenderness, rapid emaciation. These symptoms came on 2–10 days after operations on the pancreas and gall-bladder and disappeared when the patient could start eating. Hartmann (1934) stressed the importance of giving not only sodium chloride but also some potassium, calcium, magnesium, and phosphates, and used the Ringer–Locke solution. Many others, myself included (Graham, 1938), hoped that this solution would give better results, but it is now recognized that potassium is contraindicated for 24 hours or more after an operation, and that after this time the amount of potassium is too small to be of any value. Further, the proportion of sodium to potassium, 16 : 1, is so high that the action of the potassium is completely swamped by that of the sodium.

Excretion while Fasting

Since many patients are unable to take any food by mouth after serious operations, the observations which have been made on men who have fasted for 20–40 days are of importance, and I will first describe them and then discuss how the operation alters the normal reactions of the body. The

most comprehensive of these researches was carried out by Benedict in 1915, on a man aged 40 and weighing 60.1 kg., and lasted 31 days. I shall refer only to the excretion of water and nitrogen and the electrolytes in the first 14 days, though there are many other points of interest in the monograph which repay study (Table II). The amount of water given

TABLE II

Days	Intake	Output					
	Water (ml.)	Urine (ml.)	Nitrogen (g.)	Chlorine (g.)	Sodium (g.)	Potassium (g.)	Calcium (g.)
1	750	660	7·1	3·77	2·07	1·63	0·217
2–4	750	582	10·5	0·80	0·926	1·368	0·243
5–6	750	638	10·29	0·41	0·276	1·445	0·274
7–8	750	555	10·03	0·44	0·154	0·883	0·253
9–10	750	636	10·40	0·30	0·128	0·944	0·237
11–12	900	540	10·19	0·33	0·10	0·975	0·219
13–14	900	604	10·49	0·29	—	—	0·226
15–16	900	823	9·02	0·15	0·109	0·814	0·250
30–31	900	566	6·94	0·13	0·053	0·606	0·138

to drink was 750 ml. daily for the first ten days, and the volume of the urine was about 600 ml. daily. Although the man did not complain of thirst the intake was raised to 900 ml., and four days later the output rose to over 800 ml.; the average output in the last 10 days was 688 ml. The excretion of nitrogen before the fast was 11.54 g. and after an initial drop to 7.1 g. the average output for the second to fourth days was 10.5 g.; it then remained fairly steady above 10 g. up to the fourteenth day, when a sudden drop occurred to below 10.0 g. The small excretion on the first two days is ascribed to the sparing effect of the glycogen in the body. After the third day the nitrogen excretion must come solely from the breakdown of the muscle and other cells.

The excretion of chlorine, sodium, and potassium is higher on the first day than on the next three days, and this is thought to be due to the amount in the previous diet. The figures for the second to fourth days show that more potassium is excreted than sodium and that after the sixth day the sodium and chlorine decrease rapidly, while the potassium remains high. The muscles and other tissues of the body which are used up in a fast contain very little sodium, and this explains the great decrease in the output, though it is known that the kidney tubules are able to reabsorb some sodium and so reduce the amount lost from the body. The potassium excreted in the urine comes almost entirely from the breakdown of the muscle and other cells, and the N : K ratio is thought to be about 10 : 1. In Benedict's case the N : K ratio was 10 : 0.77 on the second to fourth days; altered to 10 : 1.1 on the seventh to ninth days, and then slowly changed to 10 : 1.21 on the 31st day. For a ratio of 10 : 1 on the second to fourth days the potassium excretion should be 1.05 g. instead of 1.368 g., so that rather more potassium was being excreted than the ratio allows; while on the 31st day 0.606 g. was excreted instead of 0.734 g. This decrease in the potassium excretion might be due to the broken-up muscle containing less potassium at the end of the fast or to the tubules of the kidney reabsorbing more of the potassium and so conserving it in the body; the latter hypothesis seems the more likely.

Metabolic Changes Following Shock

When an operation is performed the shock which may occur alters the metabolism of the patient very profoundly.

(1) Water Output

The fluid intake, 900 ml., with an output of urine of 700–800 ml., is much too small for patients after operation. Thus, Maddock and Coller (1937) have estimated that the water lost by the skin and lungs after operation varies from 1,000 to 1,500 ml. a day, and this amount will be increased by, say, 500 ml. if fever is present. The healthy kidney can excrete all the electrolytes in 500 ml., but the damaged kidney needs 1,500 ml. to achieve the proper excretion. Avery Jones and Naunton Morgan (1938) have also stressed the importance of giving plenty of fluid, 3,000–3,500 ml., to patients after operation, and of increasing this amount to make up for the loss of fluid vomited or removed from the stomach after severe abdominal operations. They also stress the danger of giving too much salt in uncomplicated cases. Le Quesne and Lewis (1953) gave patients a fluid diet containing 4,000 ml. before operation, and the urine output decreased from 3,195 to 1,115 ml. (average of 15 cases) on the day of the operation. Hence the fluid intake after operation should be 1,500–2,000 ml. for the afebrile patient with healthy kidneys, and 3,000–3,500 ml. for the febrile patient with poor kidneys. If sulphonamides are required, an output of more than 1,000 ml. is necessary to prevent any ill effects in the urinary tract.

(2) Protein

If a patient after operation takes very little food there is bound to be much destruction of protein, such as occurred in Benedict's starving man. This may amount to 7–10 g. a day, and will coincide with the excretion of 1 g. or so of potassium a day. If, however, the patient is able to take the same diet on the operation and subsequent days as he did before operation, the extra nitrogen loss is so small that it does not seem that the operation causes any destruction of body protein (Werner *et al.*, 1949).

(3) The Electrolytes Sodium and Potassium

The effect of the operation on the sodium and potassium is to cause a considerable increase in the potassium excretion but a decrease in the sodium excretion. The increase in the potassium excretion is to be expected from the increased protein breakdown due to lack of food, but it is much greater than could be expected from this cause, and the paradoxical condition may arise in which the serum potassium may be very high at a time when the potassium in the muscle has been greatly depleted. This discrepancy is due to the kidney being unable to excrete the extra potassium. The giving of sodium as isotonic saline in amounts of from 9 to 27 g. of sodium chloride, which has been the current practice for so many years, has obscured the fact that, coincident with the increase in the potassium excretion, there is a decrease in the sodium excretion. This change has been studied by Tabor and Rosenthal (1945). They applied a tourniquet to one leg of a mouse for two hours, and estimated the change in the injured and uninjured muscles. One-third of the potassium left the muscles and was replaced by sodium. The excretion of potassium in the urine was greatly increased, but in spite of this the serum potassium was also increased. The excretion of sodium, on the other hand, was decreased and sodium chloride given intravenously might be retained. Fox and Baer (1947) repeated these observations on a rat and analysed the tissues four hours later (Table III).

TABLE III

	Sodium in Muscle		Potassium in Muscle		Sodium and Potassium	Na/K Ratio
	mEq/kg. Water	mg./100 g.	mEq/kg. Water	mg./100 g.	mEq/kg. Water	
Normal	81±3	186±5·75	126±3	492± 7·8	207±3	0·644 : 1
Shock leg	142±2	327±4·6	48±3	187±19·5	190±4	2·96 : 1
Opposite leg ..	77±4	177±9·2	133±3	520±11·7	210±4	0·578 : 1

This experiment shows a great reduction in the potassium and its replacement by sodium, and a change of the sodium/potassium ratio from 0.644 : 1 to 2.96 : 1. They also estimated the sodium space by means of the radio sodium and radio bromide method, and found that the sodium was much increased. Darrow (1945) showed that half the potassium might leave the muscles and that the intracellular sodium was equal to one-half the extracellular sodium. This was the case in animals, and he thought that similar, if less marked, changes occurred in man. Both the above pairs of workers observed that the mice were very ill after removal

of the tourniquet, and Tabor and Rosenthal produced symptoms of potassium poisoning by injecting small amounts of potassium. They were able to prevent death in shock by giving isotonic saline by mouth or through a stomach tube in 24 hours in a volume equal to 10 or 15% of the body weight. In severe cases it was necessary to give it intravenously. If only a volume equal to 5% of the body weight was given the percentage recovery was less (10% of the body weight in a man of 65 kg. would be 6,500 ml.). A 5% solution of glucose gave little better results than in the controls, but a 10% solution of glucose was not used. These amounts per kg. are much more than those used in man, and the shock produced must have been very great. The increase in the amount of sodium in the muscles and the decrease of potassium seemed very surprising, as it had been believed that the sodium could not enter the cells. But Darrow (1945, 1946) showed that sodium could cross the cell membrane and enter the cells and that potassium left them. This effect can be produced by giving sodium chloride intravenously, and as much as half the potassium may leave the cell.

It had previously been shown by Fenn and Cobb (1936) that when the muscle of the rat was stimulated for three hours, at a frequency of over 400 a minute, the potassium in the muscle decreased greatly, while the sodium increased. When the muscle was allowed to recover for two hours the potassium increased slowly while the sodium decreased rapidly. These observations on animals have been confirmed in patients after operation. Idris Evans (1950) showed that the amounts of sodium and potassium present in muscle were altered after operation (Table IV).

TABLE IV

		Muscle Removed at Operation		Serum Potassium	
		mEq/kg. Wet Muscle	mg./100 g. Wet Muscle	mEq/ litre	mg./ 100 ml.
Case 1	Sodium	39·2	90		
	Potassium	72·4	282	3·63	14·2
„ 2	Sodium	46·5	107		
	Potassium	41·3	161	1·7	6·65

Both the sodium space and the bromide space after operation have been investigated by Eliel *et al.* (1950), by injections of radio sodium and radio bromide. They found a great increase in the sodium space—showing that sodium had entered the muscles—and a decrease in the bromide space. Another consequence of the migration of the sodium is that there may be insufficient sodium to combine with bicarbonate, and a persistent hypochloraemia may result. The sodium/potassium relation in muscle is also upset by injections of deoxycortone. Darrow and Miller (1942) injected 2–4 mg. a day into rats for 30 days, and showed that the potassium in muscle decreased from 48.9 to 38.4 mEq per litre (191 to 150 mg. per 100 ml.) per 100 g. of fat-free solids, and that areas of necrosis occurred in the cardiac muscle, which resembled those produced by low-potassium diets.

When a dog is injected with 25 mg. of deoxycortone daily for four weeks it develops a polyuria at once, and, after some time, weakness and finally a paralysis of the muscles (Ferrebee *et al.*, 1941). The potassium in the serum decreased from 4 to 2.9 mEq per litre (15.6 to 11.4 mg. per 100 ml.) after four weeks; the sodium and chlorine increased slightly. The potassium in the muscle decreased from 82.5 to 54 mEq per litre (325 to 211 mg. per 100 ml.) per 100 g. of fat-free muscle in one experiment, while the sodium increased from 33.9 to 55.6 mEq per litre (78 to 128 mg. per 100 ml.) and the chlorine from 24.7 to 26.6 mEq per litre (87.6 to 94.5 mg. per 100 ml.). Eliel *et al.* (1950) have suggested that the surgical trauma increases the production of A.C.T.H. from the pituitary fluid, and this stimulates the adrenal cortex and is thus responsible for the excretion of the potassium and retention of the sodium. MacPhee (1953) also thinks that these "electrolytic charges are the result of increased adrenocortical activity" and "are the natural response of the body to trauma." These observations suggest that the use of deoxycortone after operation is contraindicated, since the changes in the potassium and sodium of muscles are similar to those which occur two to four days after operation.

Effects of Potassium-deficient Diets

The changes which occur in the potassium after operation, and the symptoms which may arise, are so remarkable that the effect of diets containing little potassium has been studied on rats, dogs, and man. Follis *et al.* (1942) observed the effects in rats. After the 15th day opaque white areas could be seen macroscopically beneath the epicardium. Mioroscopically, definite changes could be seen as early as the eighth day. These were a loss of structure of individual muscle fibres and a failure of the hyaline fibres to stain with eosin. By the 15th day the opaque areas were shown to be necrotic and the heart muscle contained 35% less potassium than the controls. The skeletal muscle did not show any change, but the first convoluted tubules of the kidneys were dilated and the cells were vacuolated. Dogs kept on low-potassium diets developed periodic paralysis and respiratory failure, which was made worse if excess of sodium was given. On microscopical examination the myocardium was unaffected, but a waxy degeneration of the skeletal muscle was present.

The effect of a diet containing little potassium has been studied by two pairs of workers in England. A diet was given from which the potassium had been absorbed by means of an exchange resin "zeo-karb 225 sodium" (Black and Milne, 1952a, 1952b), or the resin was eaten with a fixed diet (Fourman and Ainley-Walker, 1952). Black and Milne's experiments lasted six to seven days, and a loss of 268 and 289 mEq (10.48 and 11.3 g.) of potassium was observed. A metabolic alkalosis was produced and the serum potassium decreased from 4 to 3.1 mEq per litre (15.6 to 12.3 mg. per 100 ml.) and 3.2 mEq per litre (12.5 mg. per 100 ml.), but the potassium in the red cells was unaltered. The symptoms observed were a little general apathy. The only change in the E.C.G. was the appearance of a U wave. Fourman and Ainley-Waker's three experiments lasted longer, 12 and 11 days, and the negative balance for potassium varied from 338 to 839 mEq per litre (13.2 to 32.8 g. per 100 ml.) and in their cases a slight acidosis instead of a metabolic alkalosis occurred. The subjects felt and looked ill, became absent-minded and then confused, and one developed oedema of the face and legs. The change in the E.C.G. was the appearance of a prominent U wave. Black and Milne pointed out that the amount of potassium lost was about equal to that lost after an operation, and doubted whether the symptoms occurring after operation were due to the lack of potassium. If these experiments are repeated it would be of great interest to determine the sodium and bromide space and also the amount of potassium and sodium in the muscle tissue. The injection of 18 g. of sodium chloride a day intravenously might also intensify the symptoms, since some of the sodium might enter the cells and increase the loss of potassium. The giving of glucose and insulin might produce great weakness or even paresis of the limbs like a periodic paralysis. This sometimes occurs after serious operations.

The changes which occur as a result of intravenous injection of sodium chloride before and after operation have been studied by Marks (1950). He carried out a complete water, nitrogen, chlorine, sodium, and potassium balance for three days on a patient with pyloric obstruction before operation. The actual amounts of fluid and electrolytes given intravenously varied from day to day, and the figures are given for the three-day period in Table V. The amounts excreted in the urine or removed from the stomach by suction were measured, and enable a proper balance to be struck.

Table V shows that there was an apparent positive balance of 1,020 ml. of fluid in the three days. But no allowance is made for the loss of fluid from the skin and lungs, and it is probable that a negative balance of more than 2,000 ml.

TABLE V

	Intake for 3 Days	Output for 3 Days					
		Urine		Gastric Contents Obtained by Suction		Balance	
Fluid	10,850 ml.	4,390 ml.		5,440 ml.		+1,020 ml.	
	mEq g.	mEq	g.	mEq	g.	mEq	g.
Sodium	907 20·86	134	3·08	191	4·39	+582	+13·39
Calculated as sodium chloride	53·0		7·83		11·2		34·0
Potassium	7·4 0·29	156	6·1	37	1·45	−185·6	−7·25
Calculated as potassium chloride	0·55		11·6		2·76		−13·8
Nitrogen	7·2		36·5		4·4		−33·7

occurred in the three days in spite of the large intake of fluid. This was due to the large amounts of fluid removed from the stomach, which amounted to 5,440 ml. in the three days. It is now recognized that the fluid vomited or removed from the stomach or intestine by suction should be measured and an equivalent volume added to the intravenous injection so as to ensure that the body does not suffer from lack of water. Since some potassium as well as sodium is lost from the stomach, the intestines, and biliary tract, the appropriate solutions for each tract should be used (Darrow, 1945). The chlorine and sodium figures show that a retention of 13.39 g. of sodium or 34 g. of sodium chloride occurred in three days, while there was a loss of 7.25 g. of potassium or 13.8 g. of potassium chloride. The nitrogen intake was very small and a loss of 33.7 g. occurred in the three days, which would account for a loss of 3.37 g. of potassium, leaving 3.88 g. of potassium unaccounted for.

The changes in the blood, which occurred in the three days (Table VI), show that the treatment with saline was satisfactory in that there was a decrease from 42 to 24.1 mg. in the blood urea nitrogen, although it is still a little too high. The alkali reserve, which had been very high, was now within normal limits. The chloride, which had been on the low side, was within normal limits; the sodium content, which had been slightly on the low side, was within normal limits. The potassium, which had been normal at 4.3 mEq per litre (16.8 mg. per 100 ml.), was now very low at 2.75 mEq per litre (10.75 mg. per 100 ml.). The patient developed gastric retention after the gastrectomy and was quite ill for three weeks. Small doses of potassium chloride were given by mouth, but two and a half weeks elapsed before the serum potassium and the electrocardiograph returned to normal. Table VI shows the changes in the blood serum during the course of the treatment.

TABLE VI

Days	Blood Urea Nitrogen mg./100 ml.	HCO_3 mEq/l.	Vols. CO_2 per 100 ml.	Chloride		Sodium		Potassium	
				mEq/l.	mg./100 ml.	mEq/l.	mg./100 ml.	mEq/l.	mg./100 ml.
1	42·2	50·2	112	85	303	137·0	315	4·3	16·8
2	36·8	45·2 38·3	102 85·7	89	316	139·0 141·5	320 325	3·4 3·1	13·6 12·2
3	32·2	37·4 32·0	83·7 71·6	96	340	137·0 139·0	315	3·2 2·8	12·5 10·95
4	24·1	27·0	60·5	102	362	140	322	2·75	10·75

Another patient was studied four days after operation. Sodium was omitted and the potassium was increased to 2.34 g. in four days. The potassium excreted in the urine and that removed from the stomach in four days was 4.395 g. The negative balance of potassium was 2.005 g., which is much less than in the other patient, to whom 20.82 g. of sodium was given in four days.

Randall *et al.* (1949) have also made careful observations which show that the loss of potassium that occurs after operations considerably exceeds the amount of potassium that could possibly come from the breakdown of protein, and which emphasize the decrease in the serum potassium which occurs after three to four days. This can be prevented by giving potassium by mouth or intravenously, starting 24 hours after the operation.

Symptoms Ascribed to Hypopotassaemia

These have been analysed by Eliel *et al.* (1950) in 32 patients, and are similar to, though more severe than, those described by Whipple (1923). They consisted of lethargy, apathy, and depression, 17; nervousness, irritability, and apprehension, 7; confusion, disorientation, and delusions, 4; irregular pulse, 3; muscular twitching and tetany, 3; muscular weakness, 13; abdominal distension and cramps, 19; anorexia, nausea, and vomiting, 15; paralytic ileus, 7; shallow respiration, 7; oedema, 9 cases. When the serum potassium is less than 4.2 mEq per litre (16.4 mg. per 100 ml.) the E.C.G. shows definite changes. The T wave becomes smaller and smaller the lower the serum potassium, and may be almost absent. When potassium chloride is given intravenously the T wave reappears. Fig. 3 shows the changes in the electrocardiogram due to hypopotassaemia, and the restoration to normal after potassium has been given.

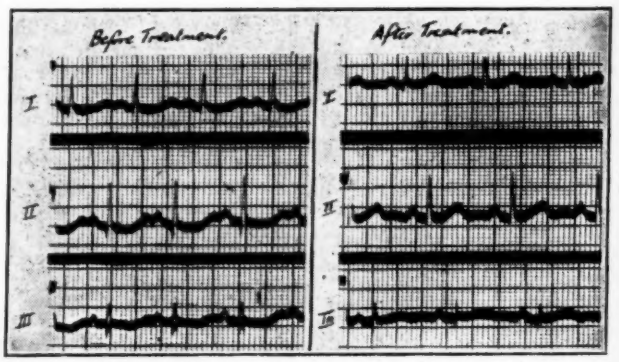

FIG. 3.—Electrocardiogram showing the changes which occur when the serum potassium is low, and after treatment with potassium.

Effect of too Much Potassium in the Serum after Operation

Ever since Ringer (1883–4) showed that the heart stopped in diastole if too much potassium was present, there has been great fear of causing potassium poisoning if any potassium was given intravenously, even the small amount in Ringer–Locke solution. This fear has been intensified by the work of Winkler *et al.* (1939). They showed that when an isotonic solution of potassium chloride was injected into a 21-kg. dog at a rate of 112 mg. a minute the dog died in 50 minutes after 5.96 g. of potassium chloride had been injected. In this time the potassium in the serum increased from 4.1 to 14.7 mEq per litre (16 to 57.5 mg. per 100 ml.). Death occurred with the heart in diastolic arrest, and the E.C.G. showed characteristic changes—an increase in the amplitude and a shortening of duration of the T wave. This occurred in a concentration of 5 to 7.8 mEq per litre (19.5 to 30.6 mg. per 100 ml.) and the T increased in size until it equalled that of the QRS complex. Later the ST segment dropped below the isoelectric line, and the QRS complex became wider and finally completely disorganized. The critical concentration seemed to be 14–16 mEq per litre (55–62.5 mg. per 100 ml.), or nearly four times the normal figure. Fig. 4 shows the changes in the electrocardiogram due to hyperpotassaemia.

Three points in that paper seem to have escaped general notice: (1) If this amount was given slowly to healthy dogs no ill effects occurred. (2) The effect of adding glucose to the solution was not tried. The glucose would have enabled the muscles and liver to lay down more potassium with the glycogen and thus reduce the amount of potassium in the serum more rapidly. (3) The equivalent amount of potas-

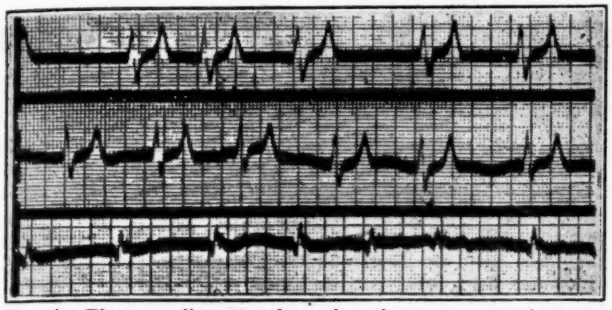

FIG. 4.—Electrocardiogram taken when the serum potassium was 10.3 mEq per litre (40 mg. per 100 ml.).

sium chloride for a man of 65 kg. is 19.3 g., which is rather more than has been suggested even for patients suffering severely from hypopotassaemia.

It is very remarkable that these experiments on healthy dogs should have deterred many workers from using potassium in the past and should still frighten some. Since the giving of potassium is regarded by many as a dangerous procedure it is important to consider how much potassium is present in the blood and extracellular and intracelluar fluids. If 1 g. of potassium (1.9 g. of potassium chloride) is quickly given intravenously to a man weighing 65 kg. whose serum potassium was 4.5 mEq per litre (17.6 mg. per 100 ml.) the maximum increase would be 12.3 mEq per litre (48.4 mg. per 100 ml.), which would be nearly a poisonous dose. But if the solution was given slowly, say in eight hours, the potassium would enter the extracellular fluid and then the intracellular fluid, and some would be excreted in the urine. The maximum rise would be 2 mEq per litre (7.8 mg. per 100 ml.) if the extracellular fluid alone was entered, and 0.56 mEq per litre (2.2 mg. per 100 ml.) if it was spread equally over the intracellular fluid. It follows that if the potassium is taken up equally by the extracellular and intracellular fluids of a 65-kg. man, a deficit of 1 mg. per 100 ml. in the serum potassium will mean a deficit of 0.0079 g. of potassium per kg. (0.0133 g. of KCl)—that is, 0.455 g. = 0.87 g. KCl per 65 kg.

It is generally agreed by those who have found potassium valuable in post-operative treatment that it should not be given until more than 24 hours have elapsed since the operation, when the kidneys have recovered their power of excreting water and the chance of a retention of potassium in the blood has passed.

Symptoms due to Hyperpotassaemia

These have been described in patients with renal failure (Finch *et al.*, 1946). The patient rapidly develops a true paralysis of two or four limbs, with shallow, laboured breathing. The reflexes are absent, but sensation of pain is present though numbness of hands may occur. The condition is said to resemble a Landry's ascending paralysis. The heart sounds are characteristically "dulled, prolonged, as if the heart were beating in slow motion"; bradycardia is present, with frequent irregular pauses. Bull *et al.* (1953) have also reported the rather sudden onset of paralysis in three patients with uraemia. At first sight the symptoms of hyperpotassaemia resemble those due to hypopotassaemia. But in the latter they develop slowly several days or more after the patient has been operated on. Again, the condition of the limbs is described as a weakness rather than a paralysis such as occurs in hyperpotassaemia. These differences should be enough to make a differential diagnosis easy after an operation. Thus, hyperpotassaemia may occur after a severe operation if the kidney fails to excrete the potassium liberated from the muscles.

Eliel *et al.* (1950) found one patient with a serum potassium of 12.2 mEq per litre (48.5 mg. per 100 ml.) on the day after operation, and Tabor and Rosenthal (1945) noted that mice were very sensitive to injections of small amounts of potassium some hours after the tourniquet had been removed from the leg. Any risk of this occurring should be past by 24–36 hours after operation, provided sufficient water, sodium chloride, and glucose are given. In the next two to six days hypopotassaemia may develop, and any weakness of the limbs occurring at this time must be due to the lack of potassium, which can be confirmed by the flat T wave in the E.C.G., and a serum potassium which may be very low. This condition must be treated with potassium, and the weakness of the limbs will soon disappear. If, now, paralysis of the muscles develops suddenly in a patient who is receiving or has just finished a potassium injection, the condition can safely be diagnosed as due to hyperpotassaemia. The fact that paralysis or weakness of the limbs occurs both with excess and with lack of potassium seems extraordinary, but there is a parallel in diabetes mellitus, in which coma develops, owing to ketosis, when insulin is lacking, but also when insulin is in excess, owing to the lack of sugar in the blood. In this case, also, the history of the onset is of value, since when insulin is lacking the coma develops slowly, whereas when insulin is in excess the coma develops very rapidly. Thus in both hyperpotassaemia and hyperinsulinism the treatment consists in giving glucose as soon as the diagnosis is made.

Treatment for a Dangerous Hyperpotassaemia

An immediate injection of 20–30 units of insulin should be given, followed by 50 g. of glucose by mouth, or, in an emergency, by injection of 1,000 ml. of 10% glucose (Bywaters, 1944; Bull, 1951–2). This will cause an immediate deposit of glycogen and potassium in the liver and muscle (Fenn, 1939) and will cause a reduction in the serum potassium. Bull (1951–2) has reported a case of anuria in which the potassium was 10 mEq per litre (39.1 mg. per 100 ml.), and two hours after the giving of 50 g. of glucose intravenously and 50 units of insulin, the potassium had decreased to just over 7 mEq per litre (27.4 mg. per 100 ml.) and the character of the T wave of the E.C.G. was much less abnormal. But the action of the glucose can only be temporary, for as soon as the glycogen is needed for energy requirements the potassium will be liberated and will again enter the serum. It is probable that by this time, 6–12 hours, some of the potassium will already have been excreted in the urine, unless renal failure is present. If necessary the glucose and perhaps the insulin can be repeated in eight hours, but the possibility of hypoglycaemia occurring must be remembered, and the blood sugar estimated before more insulin is given. Darrow and Pratt (1950) found that a calcium injection was as useful but had a temporary effect only. To be of real value the dose of calcium necessary to neutralize the poisonous action of potassium would also have to be a poisonous one (Ringer, 1884–5), and after the potassium excess had passed the calcium might cause equally serious symptoms. If it is known that the serum calcium is definitely lowered, 1–2 g. of calcium gluconate should be given intravenously, and 1–2 g. of calcium carbonate given by mouth every four hours if vomiting is not present, together with 10,000 units of calciferol or 3.75 mg. of tachysterol by mouth to ensure the absorption of the calcium from the gut.

Pre-operative Treatment

It is important to consider how the patient should be prepared for operation so as to steer between the Scylla and Charybdis of too much and too little potassium. The diet taken by patients with a good appetite contains about 3 g. of potassium, but patients who are being strictly dieted for a gastric ulcer with, say, 20 oz. (570 ml.) of milk, 25.6 mEq (1 g.) K; 3 eggs, 5.27 mEq (210 mg.) K; 2 oz. (57 g.) of biscuits, 2.56 mEq (100 mg.) K; 3 oz. (85 ml.) of orange juice, 3.84 mEq (150 mg.) K, will take 37.4 mEq (1.46 g.) K daily. If an oesophageal or pyloric obstruction is present the amount of potassium imbibed may be very much less, and a diarrhoea or a biliary fistula (Darrow, 1948) will cause great loss of potassium. In this type of case 1 g. of potassium should be given three times a day in order to ensure that the body has a proper store of potassium. The serum potassium should be estimated and an E.C.G. taken. The following amounts of potassium salts each contain

approximately 1 g. of potassium and can be taken in 30 ml. (1 oz.) of orange juice and water.

Potassium chloride, 1.91 g. = 1 g. K = 25.6 mEq K

Dipotassium hydrogen phosphate, 1.36 g.
Potassium dihydrogen phosphate, 1.36 g. } = 1 g. K. = 25.6 mEq K

Potassium citrate, 1 g.
Potassium acetate, 1 g.
Potassium bicarbonate, 1 g. } = 1.15 g. K = 29.4 mEq K

If a patient is vomiting, or is unable to swallow, the potassium should be given intravenously. Before this is done the serum potassium and the size of the T wave should be determined. If these show a definite lack of potassium, 1 g. of K (1.9 g. KCl) in 1,000 ml. of 5% glucose in distilled water should be given intravenously in eight hours twice a day until the serum potassium and the T wave are within normal limits. An operation should not be performed, except in an emergency, until the serum potassium and the other electrolytes are within or nearly within normal limits. This procedure might reduce the necessity for gastric and duodenal suction after the operation.

Post-operative Treatment

From what has been said already it is plain that the problem is very complex, and the correct treatment varies according to the degree to which the sodium and potassium balance has been upset (1) by the "shock" of the operation; (2) by the treatment necessary to combat the effects of the "shock"; and (3) by the rapidity with which the serum potassium returns to normal, making it possible to give adequate amounts of potassium and so enable it to re-enter the muscle cells and displace the sodium. In most patients the "shock" of the operation is not serious. Soon after recovery from the anaesthetic the patient may be able to take fluid by mouth, and an effort should be made to give some 3,000 to 3,500 ml. a day. The next day some food may be given, and, since this will contain potassium, the chances of a serious lack of potassium developing is negligible. If fluid cannot be taken by mouth (or this is not considered desirable) it should be given per rectum—2,000–3,000 ml. If fluid only is needed, tap-water is probably the best, as it does not seem to irritate the rectal and sigmoid mucous membrane and is well absorbed. Avery Jones and Naunton Morgan (1938) have found that one-fifth isotonic saline is well tolerated, and 3,000 ml. will contain 5.4 g. of sodium chloride, which is adequate for patients in whom the "shock" is slight and in whom food containing both sodium and potassium will soon be eaten. The shock of the operation and the 5.4 g. of sodium chloride will have probably displaced little potassium from the intracellular space, and as soon as food containing potassium is taken by mouth the convalescence should be smooth. When the "shock" is more severe it may be necessary to give the fluid intravenously, since more sodium chloride will be needed than can be absorbed from the sigmoid and colon. The volume of intravenous fluid should be 3,000–3,500 ml., but the amount of sodium chloride given must depend on the assessment of the degree of "shock" which has occurred. If 9 g. of sodium chloride is needed, the 3,000 ml. can all be given as one-third isotonic saline, with 5 or 10% glucose; if 18 g. is needed, 2 litres of isotonic saline and glucose and 1 litre of 10% glucose; while if 27 g. is needed, it can all be given as isotonic saline with 5 or 10% glucose. Any fluid recovered from the stomach and intestines must be added to the volume given as I have already pointed out. The composition of this additional fluid depends on whether the fluid lost comes from the stomach or intestines, since the amount of potassium lost directly in this way varies (Darrow, 1945). Cooke and Crowley (1952) have suggested the use of two solutions for this purpose.

For loss of gastric fluid:

	mEq			g.
Ammonium	70	or	Ammonium chloride	3.74
Sodium	63		Sodium chloride	3.68
Potassium	17		Potassium chloride	1.27
Chlorine	150			

Water to 1,000 ml.
Sodium to potassium, 3.7:1

For loss of intestinal fluid:

	mEq			g.
Sodium	138	or	Sodium chloride	5.15
Potassium	12		Sodium lactate	5.6
Lactate	50		Potassium chloride	0.895
Chlorine	100			

Water to 1,000 ml.
Sodium to potassium, 11.5:1

Some 24 hours after the operation, when the "shock" is over and the urine output good, an assessment of the case is necessary to determine how much sodium chloride is necessary and when the potassium can be started to replace that which has been lost from the intracellular space. In these severe conditions it is usually impossible to give the potassium by mouth, and there is no evidence at present that it is absorbed per rectum. It is necessary to give it as an isotonic solution with 5% glucose either subcutaneously or intravenously. If the hypopotassaemia is not very marked a mixture of sodium and potassium chloride can be given, and that used by Randall *et al.* (1949) seems suitable. After 24–36 hours, if the patient is not seriously ill they give:

110 mEq sodium, 2.53 g.
30 mEq potassium, 1.172 g.
140 mEq chloride, 4.87 g. } or { Sodium chloride, 6.44 g. / Potassium chloride, 2.44 g. / Glucose, 50 g.

Water to 1,000 ml.

This gives a proportion of sodium to potassium of 2.16:1, compared with 16:1 in Ringer–Locke solution. Either 2,000 or 3,000 ml. is given in the day. If the patient is more seriously ill and the serum potassium is already low and the E.C.G. suggests a hypopotassaemia Randall *et al.* give:

30 mEq potassium, 1.173 g.
30 mEq chloride, 1.066 g. } or potassium chloride, 2.24 g.

In 1,000 ml. of 5% glucose.

Two or three litres is given, depending on serum potassium and the E.C.G.

Conclusion

I spoke earlier of steering between Scylla and Charybdis, and I would like to elaborate the point. During the period after the operation, when the serum potassium may be high, it is necessary to steer away from the Scylla of hyperpotassaemia and towards Charybdis, using plenty of water, salt, and glucose, but as soon as the danger of being wrecked on Scylla is passed, and Charybdis with its low serum potassium and ileal stasis is being neared, the helm must be put over for Scylla, using water, potassium, and glucose, and either greatly reducing or omitting the sodium altogether. In this way the ship will slip easily between these two hazards and reach port safely—that is, the patient will make a rapid recovery. To ensure the proper co-ordination of treatment of these difficult cases it is necessary to have a team consisting of a surgeon and a physician, who should both have a real appreciation of the physiological principles involved. They should be able to call on the electrocardiograph department and on the biochemist for the essential determinations which govern the treatment. The registrar, house-surgeon, and nursing staff should appreciate the difficulties which may arise and report them promptly. The giving of potassium injections should not be left to the night nurse, and if it is necessary to do so at night a senior person should be responsible.

I have here been concerned with the changes which take place in the sodium and potassium in the body. The work on Addison's disease has shown that the sodium in the body is controlled by the hormones of the adrenal cortex. If they are deficient, the sodium in the blood decreases. At present there is no direct evidence on how the potassium is controlled, though it is clear that the sodium and potassium are closely linked. The giving of deoxycortone causes an excretion of potassium in the urine (Ferrebee *et al.*, 1941; Darrow and Miller, 1942) and the giving of potassium to a patient with Addison's disease causes an excretion of sodium. The conditions under which hypopotassaemia occurs are "surgical shock," diarrhoea due to any cause, loss of bile (Darrow, 1945), and periodic paralysis, and all these can be

successfully treated with potassium salts. A syndrome associated with cardiac symptoms, muscular weakness, and hypotension has been described by Kjerulf-Jensen *et al.* (1951). The hypopotassaemia in these conditions suggests that a hormone directly concerned must be present, though where it is formed is unknown. If this indeed exists, it would seem that it is upset in surgical shock and that if and when it is known it would be of great use in preventing this condition. I realize that I am putting forward a wholly unproved hypothesis, but the analogies to the control of other electrolytes like iodine by the thyroid, calcium by the parathyroid, and sodium by the adrenal cortex are very close. I believe that each electrolyte in the body is controlled by a hormone and not by pure physical laws, and that it is only a question of time before the hormone is discovered.

I wish to thank my friends with whom I have discussed my problems: Dr. R. G. Macfarlane for the slides, Professor V. H. Mottram, Professor A. Wormall, Dr. E. F. Scowen, and especially Dr. F. Avery Jones for much assistance.

Since the Oration was delivered my attention has been drawn by Professor E. C. Dodds to the papers by Simpson *et al.* (1952) and Grundy *et al.* (1952). These show that a hormone has been isolated from the adrenal which has a specific effect on the potassium as distinct from the sodium.

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A COMPARISON OF CORTISONE AND CODEINE MEDICATION AS AN ADJUVANT TO MANIPULATION IN RHEUMATOID ARTHRITIS

A REPORT TO THE JOINT COMMITTEE ON CORTISONE AND A.C.T.H. IN CHRONIC RHEUMATIC DISEASES OF THE MEDICAL RESEARCH COUNCIL AND THE NUFFIELD FOUNDATION

A common problem in dealing with rheumatoid arthritis patients is that of flexion deformities of the knee-joints. These commonly arise during periods of rest in bed when the position of the knees has not been controlled by rest splints. In a proportion of cases these contractures cannot be corrected by conservative methods, and manipulation under a general anaesthetic is required. It was thought that the period of increased pain and disability due to the trauma of this operation might be curtailed, or even avoided altogether, by performing the operation under cover of cortisone. At the same time it would be possible to observe the effect of such treatment on the general as well as on the local reaction following manipulation, to note any general exacerbation of the disease that may sometimes, it is said, follow this procedure, and to assess the long-term usefulness of such therapy as it affects the manipulated limb and its function. Accordingly a small-scale controlled trial was set up by a Subcommittee of the Medical Research Council/Nuffield Foundation Joint Committee on Cortisone and A.C.T.H. in Chronic Rheumatic Diseases* in which four centres participated: Bath (Dr. G. D. Kersley and Mr. J. Bastow), Sheffield (Dr. H. F. West and Mr. G. Gordon), Stanmore (Dr. Harwood Stevenson and Mr. H. J. Seddon), and Taplow (Dr. E. G. L. Bywaters and Mr. G. P. Arden). The analysis of the results of the trial was made by Dr. J. T. Boyd, of the Statistical Research Unit of the Medical Research Council, London School of Hygiene and Tropical Medicine.

Type of Patient

The patients selected were between the ages of 5 and 64 years; they had been diagnosed as having arthritis beyond any clinical doubt, and had four joints or more involved. Each had a knee contracture which had been present for at least six months and was in need of manipulative correction. Patients with severe disease activity or with completely ankylosed knees were excluded.

Allocation to Treatment

After admission to the trial patients were allotted to treatment with cortisone acetate or tab. codein. co. according to instructions given in serially numbered and sealed envelopes prepared in advance in random order. Approximately half the patients were allotted to each type of therapy.

Dosage

Following five days of preliminary observation and assessment, a total of 2.15 g. of cortisone was given to 18 patients over a period of 16 days at the level of 200 mg. for the first day; 300 mg. on the second and third days; 200 mg. on the fourth and fifth days; 150 mg. on the sixth, seventh, and eighth days; 100 mg. on the ninth and tenth days; and 50 mg. on the eleventh to the sixteenth day. The drug was given by mouth in three divided doses daily.

*The members of the subcommittee were: Dr. E. G. L. Bywaters (chairman), Mr. W. D. Coltart, Dr. J. J. R. Duthie, Professor A. Bradford Hill, Dr. G. D. Kersley, Dr. F. H. Stevenson, and Dr. H. F. West.

Tab. codein. co. were given orally to 15 patients over the same period of 16 days at the rate of two tablets three times daily throughout. If any further analgesics were needed, pethidine only was used.

Technique of Manipulation and Assessment

All the manipulations at each centre were performed by the same person, who was unaware whether the patient belonged to the codeine-treated or to the hormone-treated series. The manipulation took place on the second day of therapy in the afternoon after the second 100-mg. dose on that day—that is, after a total of 400 mg. of cortisone or 10 tablets of tab. codein. co. After the manipulation the knee was placed in plaster which was bivalved for assessment at the twenty-fourth hour, the posterior shell thereafter being replaced. Assisted active movements were carried out by the physiotherapist daily after assessment and every endeavour was made to get the patient walking as early as possible. Daily assessments were made for five days prior to treatment, for five days following its commencement, and thereafter at five-day intervals for a total period of 26 days from the patient's admission to the trial. During this time the patient remained in hospital. These assessments were made by the same group of observers at the same time each day. They had, inevitably, to know the treatment. A follow-up examination was made at approximately two months from the time of manipulation on all but 6 of the 33 patients.

The assessments included (*a*) observations on the manipulated knee; (*b*) observations on another of the affected joints, usually the contralateral knee; and (*c*) assessments of general reaction.

(*a*) The observations on the manipulated knee included pain on pressure (grades 0–3), pain on active and passive movement (grades 0–3), range of movement measured between maximum flexion and maximum extension, circumference of the knee at the top of the patella, and skin temperature (the last-named was recorded in only 17 of the 33 patients).

The time taken to do five complete flexion-extensions with the heel supported on a skate in the horizontal position was used as a test of function. Observations were also included on the strength of thrust and on the time at which the patient began to walk, but these records proved not to be comparable from one centre to another and have not been used.

(*b*) Observations on an affected but unmanipulated joint included similar tests to the above, particular attention being given to pain, range of movement, and the functional test.

(*c*) The general assessments included maximal daily oral temperature (taken four-hourly for the first 10 days of the trial and thereafter twice daily), total and differential white blood cell counts, sedimentation rate (Westergren method), and haematocrit reading. These last estimations were performed twice before manipulation and subsequently at five-day intervals up to day 26. A note was made of any complications.

Results

In total, 33 cases were admitted to the trial, 18 being manipulated under cover of cortisone and 15 under cover of tab. codein. co. Initially the two treatment groups were closely similar in age and sex and also in the length of time that the manipulated knee had been contracted (Tables I and II).

TABLE I.—*Age and Sex of Patients in the Two Treatment Groups*

Age (Years)	Males		Females	
	Cortisone	Codeine	Cortisone	Codeine
<20	0	0	1	0
20–	0	0	4	3
40–	3	2	8	6
60–64	1	1	1	3
All ages	4	3	14	12

TABLE II.—*Duration of Knee Contracture in the Two Treatment Groups*

Duration (Years)	Cortisone	Codeine
<1	1	1
1–	12	11
5–	3	2
10+	1	1
Not stated	1	0
All durations	18	15

The main results of treatment are given in Table III and the Chart, which show the mean assessments of the treated joints at intervals from the start of the trial. After some slight decrease in pain after institution of treatment there is, as would be expected, a sharp increase on the day following manipulation. The mean values are, however, very similar in the two treatment groups (2.33 cortisone and 2.40 codeine for pain on pressure and 2.44 cortisone and 2.20 codeine for pain on motion). This increased pain declines somewhat in both groups during the subsequent two days, but it remains above the average pre-manipulation level and is similar under both treatments. By about day 15–16 it has returned to the pre-manipulation values in each group.

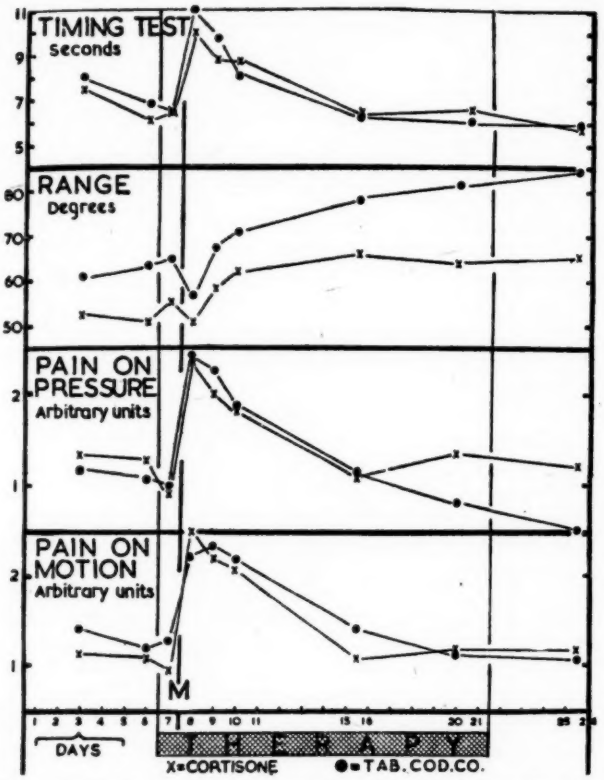
The average range of movement, which improved slightly with the start of treatment, is decreased in both groups for one day following manipulation; it thereafter immediately rises to a mean value above its original level and improves somewhat with the passage of time. If anything, the codeine group fared slightly better in this respect than the cortisone group.

The joint circumferences showed no great change throughout. The functional timing test showed, as expected, considerable lengthening in both groups following manipulation and returned to pre-manipulation levels by day 15–16. The

TABLE III.—*Joint Assessments and Sedimentation Rates at Intervals from Start of Trial (Mean Values for Each Treatment Group)*

Day*	Pain on Pressure (Arbitrary Units)		Pain on Motion (Arbitrary Units)		Range of Movement (Degrees)		Circumference of Knee (in.)		Timing Test (Sec.)		Sedimentation Rate (mm./hr.—Westergren)	
	Cortisone	Codeine	Cortisone	Codeine	Cortisone	Codeine	Cortisone	Codeine	Cortisone	Codeine	Cortisone	Codeine
1–5	1·30	1·15	1·13	1·27	52·5	60·2	14·7	14·9	7·5	8·0	24·4	19·9
6	1·28	1·07	1·06	1·20	51·7	63·1	14·6	15·0	6·1	6·8	23·3	19·9
7	0·89	1·00	0·94	1·27	55·7	65·1	14·6	15·0	6·5	6·5	—	—
(Manipulation)												
8	2·33	2·40	2·44	2·20	50·7	56·9	14·8	15·3	10·0	11·0	—	—
9	2·00	2·27	2·17	2·33	58·4	67·7	14·8	15·4	8·9	9·8	—	—
10	1·78	1·87	2·06	2·13	62·1	71·0	14·9	15·5	8·8	8·1	—	—
11											24·4	24·3
15–16 ..	1·11	1·13	1·06	1·40	65·9	78·1	14·6	15·2	6·4	6·3	14·3	24·5
20–21 ..	1·33	0·80	1·17	1·13	64·1	81·4	14·7	15·1	6·6	6·1	14·4	20·5
25–26 ..	1·17	0·60	1·17	1·07	65·4	83·9	14·7	15·1	5·8	6·0	16·5	22·8
†25–26 ..	1·27	0·50	1·20	1·08	61·3	81·3	14·7	15·5	5·3	4·8	15·5	27·1
†67±7 ..	1·00	0·83	1·33	1·17	59·8	79·8	14·8	15·2	4·8	5·0	28·2	20·4

* Days 1–5 pre-treatment; days 6–21 treatment; days 25–26 post-treatment.
† The observations in the last two lines are limited to those patients for whom observations were recorded at day 25 *or* 26 *and* day 67±7.



Joint assessment at intervals from start of trial. Mean values for each treatment group.

skin temperature over the manipulated knee rose in both groups during the two days following manipulation (Table IV), but it had subsided in both by the twenty-first day.

Analgesics (pethidine) were needed, most commonly on the day of manipulation, in approximately two-thirds of the patients in each group—namely, in 12 of the 18 patients on cortisone and 9 of the 15 patients on codeine. There was

TABLE IV.—*Mean Skin Temperature (°C.) Over Manipulated Knee* and Mean Skin Temperature Ratio†*

Day	Temperature		Skin Temperature Ratio	
	Cortisone	Codeine	Cortisone	Codeine
1–5	32·0	32·4	1·002	1·001
6	31·4	32·5	0·999	1·001
7	31·7	31·6	0·993	0·989
(Manipulation)				
8	32·8	33·1	1·030	1·022
9	33·2	33·3	1·020	1·027
10	32·9	32·7	1·041	1·031
15–16	32·5	32·3	1·030	1·012
20–21	32·3	32·7	0·996	1·001
25–26	32·0	32·1	0·997	1·021

* Based on the 9 patients on cortisone and the 8 patients on codeine for whom the necessary data were available.

† Skin temperature ratio = $\frac{\text{Skin temperature (°C.) over manipulated knee}}{\text{Skin temperature (°C.) over contralateral knee}}$

Based on data from 8 patients in each treatment group.

little evidence of any general reaction as judged by the packed cell volume, the white blood cell count, the polymorph percentage, and the sedimentation rate, although the latter fell temporarily in the cortisone-treated group. Isolated peaks of body temperature to above 99° F. (37.2° C.) occurred during the period following manipulation in five patients on cortisone and in five on codeine. Only one patient in the entire series showed a reaction in other joints (on days 23 to 26 inclusive and at follow-up on day 67). He had been treated with cortisone.

There was no marked difference between the two groups in the subsequent progress as judged from the data available on patients who were assessed at days 25–26 and also at day 67±7 (see Table III).

As would be expected, the observations on the contralateral knees which were *not* manipulated showed them, as a group, to be less severely affected than the knees chosen for manipulation. Under treatment with cortisone or codeine they showed some improvement as measured by pain on pressure, range of movement, and functional timing test recordings (Table V). On the other hand, there was

TABLE V.—*Assessment of Contralateral Knee-joints (Non-Manipulated) At Intervals from Start of Trial (Mean Values for Each Treatment Group)*

Day	Joint Assessment					
	Pain on Pressure (Arbitrary Units)		Range of Movement (Degrees)		Timing Test (Sec.)	
	Cortisone	Codeine	Cortisone	Codeine	Cortisone	Codeine
1–5 ..	0·78	0·87	89·5	92·2	6·9	7·0
6 ..	0·88	0·71	89·9	94·4	6·1	5·6
7 ..	0·71	0·64	92·5	95·1	6·1	5·6
8 ..	0·65	0·71	90·7	94·6	6·3	5·9
9 ..	0·53	0·43	93·1	97·2	5·9	5·6
10 ..	0·47	0·50	95·7	98·9	5·6	5·4
15–16 ..	0·29	0·36	94·8	98·7	5·4	5·2
20–21 ..	0·29	0·29	97·8	98·2	5·3	5·2
25–26 ..	0·53	0·36	97·4	98·4	5·1	5·0

Based on data from 17 patients in cortisone group and 14 patients in codeine group.

clearly no material difference between the cortisone-treated and the codeine-treated groups. In short, both in the manipulated knee and in the contralateral knee these treatment groups were more remarkable for the similarity of their reactions than for a dissimilarity.

Conclusion

In this investigation cortisone revealed no advantage over tab. codein. co. as a cover for manipulation of the knee. There was little, if any, systemic disturbance attributable to the manipulation in either treatment group except an occasional temperature spike which appeared equally in both groups. A general exacerbation in other joints was seen only once and could be attributable in this case to cortisone rebound rather than to the effects of manipulation. There is no evidence, therefore, that cortisone was of any greater value than tab. codein. co. given in this dosage and for this period of time as a cover for manipulative correction of contracted joints in rheumatoid arthritis.

Summary

A controlled trial has been made of the value of cortisone as a cover to manipulation of the knee-joint in patients with rheumatoid arthritis. Each patient had a knee contracture of at least six months' standing. Eighteen were treated with cortisone and 15 with tab. codein. co., this treatment being allocated in a random order. In the dosage given there was no evidence that cortisone was in any way superior to tab. codein. co. for the purpose at issue.

The Ministry of Pensions and National Insurance has compiled a large *Digest of Statistics Analysing Certificates of Incapacity, 1950*, copies of which may be obtained from the Ministry at 10, John Adam Street, London, W.C.2. The figures will not be published in the ordinary way, because they are not considered to be of sufficient general interest. They are based on medical certificates given in support of claims to State insurance benefits. Like many other statistics of this kind, they are of necessity incomplete in several respects : for instance, they do not include figures for illnesses of two or three days' duration. Moreover, the certifying medical practitioners do not always indicate the diagnosis with precision. Now that certificates are being used for statistical purposes, the Ministry hopes that doctors will show on them the cause of incapacity as accurately as possible. If the present volume is found to be useful, similar digests will be issued for 1951 and some later years.

ACTIVITY OF ERYTHROMYCIN AGAINST STAPHYLOCOCCUS AUREUS

BY

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Erythromycin is a new antibiotic derived from *Streptomyces erythreus*. Its chemical and physical characteristics were described by McGuire *et al.* (1952), and its biological properties were investigated by the same workers and by other groups (Haight and Finland, 1952a, 1952b; Heilman *et al.*, 1952). Erythromycin was found to be active *in vitro* in very low concentrations against a wide range of Gram-positive organisms, but was inactive against Gram-negative organisms with the exception of Neisseria, *Haemophilus influenzae*, *Haemophilus pertussis*, and strains of Brucella.

Erythromycin, which can be given orally, has low toxicity for man and laboratory animals; it gives satisfactory concentrations in the blood and urine but not in the cerebrospinal fluid of normal persons (Heilman *et al.*, 1952). The ability of erythromycin to protect mice against experimental infections was found to parallel the sensitivity *in vitro* of the infecting organism and to be related to the blood concentration of the drug (McGuire *et al.*, 1952). Clinical trials of erythromycin have been reported by Heilman *et al.* (1952) and by Haight and Finland (1952c). Favourable results have been obtained in various streptococcal, pneumococcal, and staphylococcal infections. Erythromycin has been shown to be particularly effective against staphylococci, whether the strains were penicillin-sensitive or penicillin-resistant (McGuire *et al.*, 1952).

There is an increasing emergence of strains of *Staphylococcus aureus* which are resistant to penicillin, streptomycin, and to one or more of the "broad-spectrum" antibiotics. The high incidence, especially in hospitals, of infections caused by such strains makes it highly desirable to have a new antibiotic at our disposal which is effective against staphylococci. Since it seems likely that this will be the chief potential role of erythromycin, the present report is devoted to laboratory experience of the drug's activity against pathogenic staphylococci.

Materials and Methods

A supply of pure crystalline erythromycin (potency 915 μg./mg.) was provided through the courtesy of Abbott Laboratories. A stock solution of the white powder was made in distilled water in a concentration of 2 mg./ml. To aid solution a little ethyl alcohol was used. This stock solution could be stored in the frozen state at −20°C for as long as eight weeks.

Many of the strains of *Staph. aureus* used were recently isolated from patients with staphylococcal infections or from normal nasal or oral flora. Stock laboratory strains were also included.

Sensitivity tests were performed with serial dilutions of erythromycin either by a tube method with digest broth as the medium or by a plate method (modified from May and Morley, 1952) with Levinthal agar. Five-hour broth cultures of organisms to be tested were obtained by picking individual colonies from the growth on blood-agar plates. In the tube test the final concentration of antibiotic ranged from 20 to 0.01 μg./ml. The inoculum was estimated to yield a final concentration of 5×10^3 organisms per ml. The sensitivity of the organism was taken to be the minimum final concentration of antibiotic that completely inhibited growth as judged by visible turbidity after 18–24 hours' incubation.

The inoculum in the plate test was one 2-mm. loopful of the broth culture (approximately 10^5 organisms). The sensitivity of the strain was expressed as the concentration of antibiotic which completely inhibited growth of the organism. The sensitivity of staphylococci to other antibiotics was estimated by a plate method (May and Morley, 1952).

In the production of resistant variants of originally sensitive strains of staphylococci two methods were employed. The first was that of Haight and Finland (1952e) in which the organism was subcultured serially at 48-hourly intervals on a series of 10% blood-agar plates containing increasing concentrations of erythromycin. The inoculum was one loopful of a broth suspension of the growth from the plate with the highest concentration of antibiotic allowing good growth. The second method was a modification of that of Barber (1953). The organism was subcultured serially on erythromycin ditch plates. These were of 10% blood agar with a ditch cut at one side of the plate and filled with the same medium containing at first 20 and later 100 μg. of erythromycin per ml. Subcultures were made from the edge of growth nearest to the ditch.

In both methods each parent strain was subcultured on antibiotic-free medium at the same intervals as the derivative strain.

Result of Experiments

Factors Influencing in vitro Sensitivity

The sensitivity of *Staph. aureus* G 1 was not affected by variations in the size of the bacterial inoculum, ranging from 5×10^8 to 50 organisms, in either the tube or the plate method. The effect of continued incubation was slight. In the tube test, incubated for 24 hours, *Staph. aureus* G 1 was inhibited by 0.25 μg. of erythromycin per ml. After 48–72 hours' incubation slight growth was visible in this tube. No new growth was visible in tubes containing higher concentrations of antibiotic.

It has been shown by Knox *et al.* (1952) that in sensitivity tests of mycobacteria with isoniazid the end-point is more unstable at some temperatures than at others, and that results obtained after arbitrary periods of incubation may vary widely. In tube sensitivity tests of *Staph. aureus* with erythromycin, variation of the temperature of incubation over a range 26–40° C. did not affect the results previously obtained.

The sensitivity of four strains of *Staph. aureus* was not affected by performing the tube test with broth to which 25% serum had been added. Plate tests with blood agar or nutrient agar in place of Levinthal agar gave identical results.

In comparative tests of 50 strains of *Staph. aureus* by the tube and plate method the results were identical with 40 strains. The sole discrepancy in the remaining 10 cases was that a scanty growth was observed on the plate corresponding in erythromycin concentration with the minimum inhibitory concentration in the tube test. On continued incubation this growth became complete, but no growth developed in plates containing higher concentrations of antibiotic.

The plate method has been adopted for routine sensitivity testing of large numbers of strains of *Staph. aureus*. Prepared

plates maintain unimpaired erythromycin potency for over two weeks after preparation if the plates are kept in the refrigerator until required.

Growth of Staphylococci in Varying Concentrations of Erythromycin

A five-hour broth culture of *Staph. aureus* G 1 was added in a final concentration estimated at 5×10^5 organisms per ml. to serial broth dilutions of erythromycin and to a tube of broth containing no antibiotic. After varying periods of incubation at 37° C., 0.1-ml. samples were taken from each tube and bacterial counts were made by the method of Miles, Misra, and Irwin (1938). At daily intervals the whole of 1-ml. samples was plated out from the tubes containing 4, 1, and 0.5 μg. of erythromycin per ml. The results are shown graphically in Fig. 1. With increasing concentrations of erythromycin the number of viable organisms remained stationary for decreasing periods of time and then declined progressively. There was no growth in 4 or 1 μg./ml. after 24 hours. With 0.5 μg./ml. complete sterilization was not achieved even after 72 hours. At lower concentrations of erythromycin the number of organisms remained almost stationary for long periods or fell slightly and then began to rise. In the case of 0.1 μg./ml. the bacterial count was almost the same as in the control culture after 24 hours.

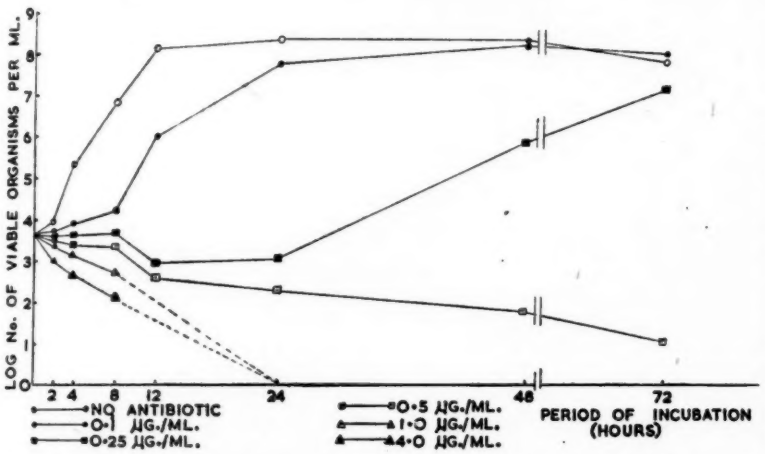

FIG. 1.—Effect of various concentrations of erythromycin (μg./ml.) on the growth of *Staph. aureus* G 1.

Sensitivity of a Large Number of Strains of Staph. aureus

A total of 213 strains were tested. All strains were coagulase-positive and fermented mannite. The distribution of sensitivity of staphylococci to erythromycin is shown in Table I. Thirty-three strains of *Staph. aureus* of known phage type were selected. These fell into each of the three main phage groups. There was no difference in erythromycin sensitivity between any of these strains. All were sensitive to 0.25–0.5 μg./ml. The sensitivity of 47 strains of *Staph. aureus* to penicillin, streptomycin, chloramphenicol, and oxytetracycline ("terramycin") was tested. The strains selected included penicillin-resistant and penicillin-sensitive organisms and strains with varying combinations of resistance to other antibiotics. All were sensitive to 0.25–0.5 μg. of erythromycin per ml. whatever their behaviour to any of the other antibiotics. The results are shown in Fig. 2.

TABLE I.—*Sensitivity of* 213 *Strains of Staph. aureus to Erythromycin (Plate Method)*

	Minimum Inhibitory Concentration of Erythromycin (μg./ml.)					
	>1	0·5	0·25	0·1	0·05	0·01
No. of strains sensitive to each concentration of antibiotic	0	157	49	6	1	0
Percentage of strains sensitive to each concentration	—	100	26·5	3·5	0·5	—

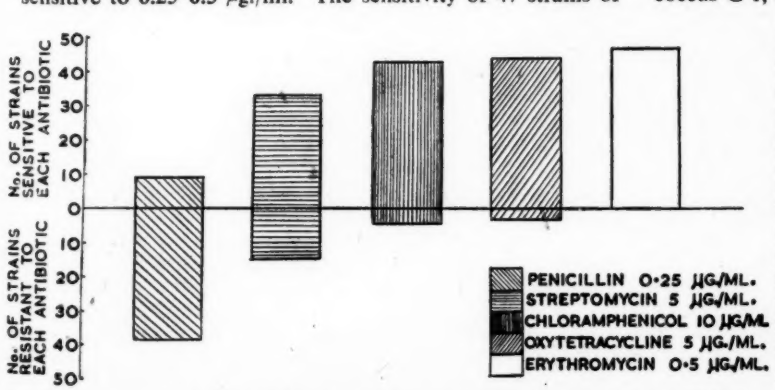

FIG. 2.—Comparative sensitivity of 47 strains of *Staph. aureus* to five antibiotics, tested by a plate method (May and Morley, 1952).

Resistance to Erythromycin

It is believed that resistance to antibiotics may develop by mutation of organisms in a "sensitive" strain to resistant forms. On contact with the antibiotic these resistant forms will be selected out. By serial subculture in the presence of antibiotic it is thus possible to develop strains whose antibiotic resistance is much greater than that of the parent. Two patterns of resistance have been described: (*a*) the penicillin pattern, in which resistance is gradual and "step-wise," depending on a series of small mutations; and (*b*) the streptomycin pattern, in which "one step" resistance of a high order can occur owing to selection of highly resistant variants in the original culture.

From an overnight culture of *Staph. aureus* G 1 a sample was taken for bacterial count and 1-ml. aliquots were spread evenly over the surface of 10% blood-agar plates containing erythromycin. Various concentrations of antibiotic were tested in separate experiments, 15 plates being used each time. The average inoculum was estimated at 2×10^8 organisms. No growth was discovered on plates containing 100, 50, 20, 10, or 5 μg. of antibiotic per ml. There was confluent growth on control plates with no antibiotic. In an experiment with 1 μg./ml., six plates gave no growth, and on eight plates a small number of colonies (2–10) appeared. On plates containing 0.5 μg. of erythromycin per ml. a variable number of colonies appeared on all plates.

These colonies could represent either mutants present in the culture or organisms which had undergone adaptation in some way during their contact with erythromycin. To decide this point the fluctuation test designed by Luria and Delbrück (1943) and adapted for work with antibiotics by Demerec (1948) was performed. From a single culture of staphylococcus G 1, small inocula (approximately 300 bacteria) were subcultured into 16 bottles of broth. After overnight incubation 1 ml. of each of 15 broth cultures was plated on to blood-agar plates containing 0.5 μg. of erythromycin per ml. From the 16th broth culture 15 samples were similarly plated (approximately 2×10^8 organisms per plate). After incubation the number of colonies on each plate was counted. The variation between plates was 15 times greater in the series of independent cultures than in the series of replicate platings of a single culture. These findings suggest that erythromycin-resistant bacteria in a culture of a sensitive organism arise spontaneously by mutation. If these bacteria originated by a process of adaptation when the culture and the antibiotic came into contact, a similar number of colonies would occur on all plates whatever the origin of the sample plated.

Development of Erythromycin-resistant Strains

Fourteen strains of staphylococci sensitive to 0.25–0.5 μg. of erythromycin per ml. were serially subcultured by the method of Haight and Finland (1952e), as described above. All the strains increased in erythromycin resistance rapidly. Two strains grew on plates containing 80 μg./ml. after only

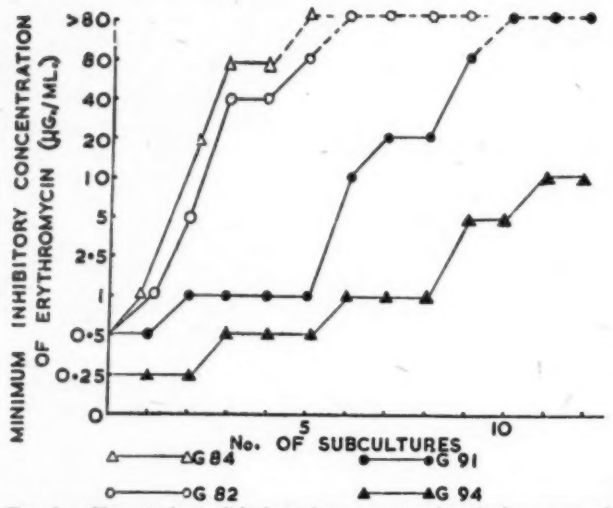

FIG. 3.—Changes in antibiotic resistance occurring during repeated subcultures of four strains of staphylococci on blood agar containing erythromycin.

five subcultures. The behaviour of four strains during 12 transfers is shown in Fig. 3. The parent strains subcultured on antibiotic-free agar retained their original sensitivity.

The resistant variants of all 14 strains of staphylococci have shown no significant change in resistance to erythromycin after 10 subcultures on antibiotic-free medium.

Metabolic Effects of Acquired Erythromycin Resistance

The 14 parent strains of staphylococci and their resistant variants were observed for colonial appearance, mannite fermentation, and coagulase production. The phage-pattern of six strains and their resistant variants was examined. None of these characteristics was changed following development of erythromycin resistance. The only

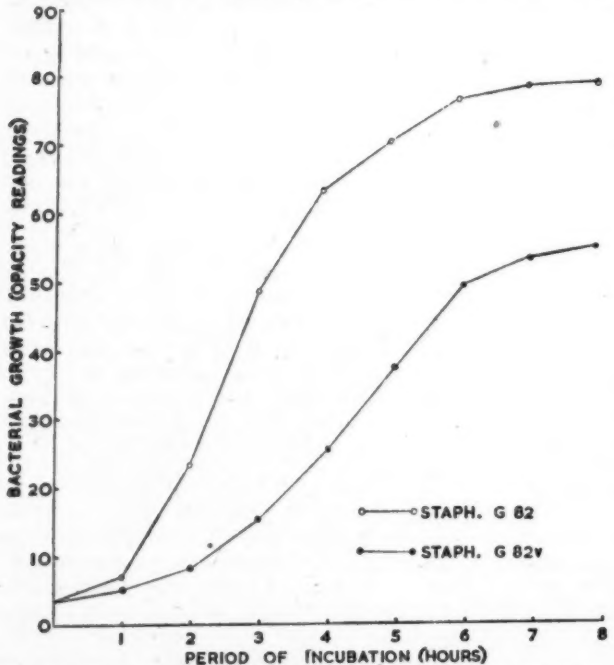

FIG. 4.—Growth curves of *Staph. aureus* G 82 and its derivative strain G 82v resistant to 80 μg. of erythromycin per ml.

difference noted was that growth of resistant variants was less active than growth of the parent strain. The growth in broth of *Staph. aureus* G 82 and its variant resistant to 80 μg./ml. was estimated turbidimetrically. The growth rate of the resistant variant was slower than that of the parent strain (Fig. 4). Each resistant variant was examined to exclude the possibility that acquired resistance might be associated with the production of an erythromycinase. The test employed for this purpose was a modification of Got's plate test for penicillinase (Haight and Finland, 1952d). There was no evidence of erythromycinase production.

The 14 staphylococci and their resistant variants were tested for their sensitivity to penicillin, streptomycin, chloramphenicol, and oxytetracycline. In no case was the development of resistance to erythromycin associated with the development of cross-resistance to any of the other antibiotics. During the course of this investigation a sample of a new antibiotic, carbomycin ("magnamycin"), was obtained through the courtesy of Messrs. Charles Pfizer, Ltd. The antibacterial activity of this agent has been described by Tanner *et al.* (1952) and by English *et al.* (1952). The range of activity of carbomycin closely resembles that of erythromycin. Cross-resistance between the two antibiotics has been reported by Finland *et al.* (1952). Four of the staphylococci used in the present investigation, and erythromycin-resistant variants selected at various levels of erythromycin-sensitivity, were tested against the two antibiotics by the plate method already described. It will be seen from Table II that increase in resistance to erythromycin was accompanied by an increase in resistance to carbomycin. Each strain tested required two to four times as much carbomycin, weight for weight, as erythromycin to produce complete inhibition.

TABLE II.—*Cross-resistance Between Erythromycin and Carbomycin*

Strain of Staphylococcus	Sensitivity of Strain (μg./ml.)	
	Erythromycin	Carbomycin
G 3	0·25	1·0
G 3v	10·0	40·0
G 6	0·5	5·0
G 6v	40·0	160·0
G 5	0·25	1·0
G 5v	80·0	160·0
G 7	0·5	0·5
G 7v	10·0	20·0

Three strains of staphylococci were subcultured serially on blood-agar plates containing erythromycin in a lateral ditch. There was a similar progressive increase in resistance, but no colonial variants were seen of the type described by Barber (1953) in her study of penicillin- and streptomycin-resistant staphylococci, nor were any erythromycin-dependent variants isolated.

Discussion

Laboratory tests with erythromycin have shown that it may be readily adapted to standard procedures used routinely for other antibiotics. The tube dilution and the agar-plate dilution methods of testing gave comparable results. Growth curves of *Staph. aureus* in varying concentrations of erythromycin show that concentrations of antibiotic higher than the minimum inhibitory concentration cause a reduction in the number of viable organisms, and may sterilize the culture, whereas with lower concentrations the organisms escape from the inhibitory effect of erythromycin after a period of bacteriostasis.

In the present study the sensitivity of 47 strains of *Staph. aureus* to erythromycin was shown to be independent of the pattern of sensitivity to four other antibiotics. Even strains which were resistant to penicillin, streptomycin, chloramphenicol, and oxytetracycline were completely inhibited by 0.5 μg. of erythromycin per ml. Sensitivity to erythromycin was also shown to be independent of phage type of the strain.

Resistance of staphylococci to erythromycin developed readily *in vitro* but appeared to follow the "stepwise" pattern of acquired resistance to penicillin rather than that of streptomycin. From the experiments described above it would appear that a culture of a sensitive strain of staphylococcus may contain spontaneous mutants which are more resistant to erythromycin. Mutants resistant to high levels of erythromycin were not found in these experiments. However, by serial subculture on media containing erythromycin progressive increase of resistance occurred in 14 strains of staphylococci tested. These strains differed from each other in the speed of development of resistance, but in no case was the first "step" to a resistance more than four times that of the original strain. Apart from some reduction in rate of growth, the biological characteristics and phage pattern of the resistant variants were unchanged. Haight and Finland (1952e) observed that development of resistance was associated with loss of coagulase activity. This finding has not been confirmed in the present study or by later experience of the same group of workers (Purcell *et al.*, 1953). Resistant variants were not found to have developed cross-resistance to any other antibiotic except carbomycin. Similar experiences have been reported by Haight and Finland (1952e) and Finland *et al.* (1952). The fact that originally sensitive strains of staphylococci rapidly develop resistance *in vitro* and also *in vivo* (McGuire *et al.*, 1952) is a potential drawback to the use of erythromycin. However, recent work (Purcell *et al.*, 1953) shows that *in vitro* combinations of erythromycin with penicillin or with streptomycin will delay or depress the emergence of resistance to both erythromycin and penicillin or streptomycin.

Summary

Methods for sensitivity testing of staphylococci with erythromycin are described. Factors affecting these tests are discussed.

The sensitivity to erythromycin of a large series of strains of *Staph. aureus* is shown to be of the order of 0.5 μg./ml., and to be independent of their phage type or their behaviour to four other antibiotics.

The effect of erythromycin on the growth rate of staphylococci has been shown to vary according to the concentration of antibiotic. Concentrations above the minimum inhibitory concentration produce a fall in the number of viable organisms.

The development in staphylococci of resistance to erythromycin appears to follow a stepwise pattern resembling that seen with penicillin.

Resistant staphylococci were found to differ from the erythromycin-sensitive parent organism only by slight differences in growth rate and by the acquisition of cross-resistance to carbomycin.

My thanks are due to Dr. R. E. O. Williams, Staphylococcal Reference Laboratory, Central Public Health Laboratory, Colindale, for performing phage-typing on the strains of *Staph. aureus* used in the resistance experiments.

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SOME LESSONS FROM 4,000 UTERO-TUBAL INSUFFLATIONS*

BY

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Personal experience of just over 4,000 utero-tubal insufflations has taught several practical lessons. The foremost lesson, in my opinion, concerns the gas employed and its safety.

Rubin's Test

Utero-tubal insufflation was first described by Rubin in 1920, so that more than 30 years have elapsed to permit the evaluation of a large number of these tests by investigators all over the world and the accumulation of recorded complications and untoward sequelae. It must not be overlooked, of course, that details of mishaps and even fatalities might pass unpublished. An illustration of this is to be found in the report of the meeting of the Section of Obstetrics of the Royal Academy of Medicine in Ireland on November 7, 1947, in which a speaker made the bald statement that he knew of eight deaths in Ireland following the Rubin test. Nevertheless, a study of the replies to Rubin's (1947) detailed questionary, returned by 356 gynaecologists and involving 80,376 insufflations, must supply the data to answer the more important questions, including the safety of the procedure. Among all these insufflations, embolism occurred in 15 patients, of whom 3 died. These deaths are additional to the 10 known post-insufflation deaths from embolism reported in the literature; Frommolt (1925), 1 case; Moench (1927), 2 cases; Mansfeld and Dudits (1934), 1 case; Weitzman and Cohen (1937), 1 case; Dible *et al.* (1938), 1 case; Feiner (1942), 1 case; Finn (1945), 1 case; and Faulkner (1946), 2 cases. In all these fatal cases air or oxygen was used; in no instance is there a record of death from embolism following insufflation with carbon dioxide. Non-fatal but alarming clinical effects, in varying degrees, have been observed by many investigators, but these are rarely seen with the use of carbon dioxide.

At the Royal Samaritan Hospital for Women, Glasgow, insufflation has been employed for nearly 25 years, and at no time has any gas other than carbon dioxide been used. The test has been carried out by various members of the staff on an aggregate of over 6,500 occasions. My personal share of these experiences amounts to just over 4,000 insufflations. None of us has seen any evidence of embolism and there certainly has been no fatality. It is reasonable, therefore, to conclude from accumulated clinical experience that carbon dioxide is the gas of choice. Moreover, it must be pointed out that Rubin, in more than 10,000 insufflations personally carried out, with the exception of approximately the first 100 cases in which he used oxygen (a procedure which was quickly abandoned by him because of the disadvantage that it takes 24–100 hours to be absorbed from the peri-

*The basis of a lecture given to Greenock and District Faculty of Medicine on March 3, 1953, at Greenock Royal Infirmary.

toneal cavity), has never used any other gas than carbon dioxide, which is rapidly absorbed. The designation "Rubin test" therefore implies the use of carbon dioxide gas only. Air has the same disadvantages as oxygen—namely, its slow absorbability and its potentiality of producing embolism, as shown in the cases outlined above. In addition, it presents a greater theoretical danger of introducing infectious material. On several occasions I have introduced varying quantities of carbon dioxide, from different types of insufflator, direct into broth culture medium; on no occasion was any bacterial growth obtained. In this connexion it may be observed that in Rubin's questionary a total of 190 pelvic infections followed the 80,376 insufflations. Of these, 38 required operative treatment. There were two deaths, both in patients in whom air had been insufflated. I have had five pelvic infections in over 4,000 insufflations with carbon dioxide. Three were mild and two severe; one of the latter required operation. Not one was fatal.

Use of Air in Insufflation

It is of interest to retrace briefly the steps by which air came to be introduced for the purpose of insufflation. Furniss (1921) reported a simplification of the Rubin test and suggested that the method might be still further simplified by using air instead of carbon dioxide. Jacoby (1923), acting on this suggestion, was the first to report the use of air. He claimed that it had the following advantages: it eliminated the necessity for having on hand cumbersome tanks of gas with other attachments; there was no possibility of air being exhausted, as occasionally happens with tanks when a test is in progress; being more compact, the apparatus is readily portable should occasion arise; there is no expense or inconvenience in replacing tanks; the air is free and always obtainable. In 40 cases Jacoby found no evidence of any serious infection, and added that there is no reason to expect infection as a result of the introduction of air, since in every laparotomy air enters the peritoneal cavity with no untoward results. In the following year Victor Bonney (1924) described his simplified air apparatus, involving the use of a cannula, of the size of a No. 7 dilator, and a manometer. He stated that it had been previously pointed out to him by Arthur Gray that an elaborate apparatus was not necessary and that equally reliable results could be obtained by injecting air by means of a simple rubber bulb, attached to which was a metal tube furnished with a rubber obturator.

It is obvious, therefore, that air was introduced for insufflation solely for the purpose of simplification of procedure, which meant, essentially, the elimination of the necessity for a bulky cylinder of carbon dioxide or oxygen and a heavy and not easily portable apparatus. To-day, this reason is not valid, since several types of portable insufflation apparatus employing carbon dioxide are available. Moreover, Jacoby's argument that the use of air must be safe, as it enters the peritoneal cavity at every laparotomy, is fallacious, since in utero-tubal insufflation the circumstances are very different. In the latter procedure air is forced under positive pressure into the uterine cavity, from which it can escape only through the tiny tubal lumina and not even therefrom in cases of non-patency. The circumstances are not the same, however, in Decker's test of tubal patency, in which a uterine cannula is introduced when the patient adopts the knee-chest position: air then enters under negative pressure. According to Finn (1945), the two prerequisites for the development of an air embolism are (1) a vessel which is in a state of incomplete collapse, and (2) the introduction of air under positive pressure into the circulation. These conditions are present, in varying degree, in tubal insufflation with air, especially when associated with curettage. The embolism is of the venous type, air entering the peripheral veins and flowing by means of the vena cava to the right side of the heart and thence to the pulmonary arteries.

Further consideration of the possibility that in utero-tubal insufflation the gas used might enter the blood stream via uterine veins may now be given on the lines of accepted physiological fact and also on experimental lines. On general physiological principles, air (with its high nitrogen content) is thoroughly dangerous; oxygen is less dangerous because of the affinity of haemoglobin with the gas, and carbon dioxide infinitely the safest. The solubilities of nitrogen, oxygen, and carbon dioxide in millilitres per 100 ml. of blood at 38° C. and 760 mm. of mercury pressure are 1.1, 2.3, and 54.1 respectively (Samson Wright, 1945). Indeed, owing to the high capacity of blood for carbon dioxide it is generally accepted by physiologists that it must be almost impossible to produce carbon dioxide embolism. It is well known that the latter gas is rapidly absorbed and eliminated through the lungs. This rate of absorption is probably as high as 250 ml. per minute (Van Slyke and Gross, quoted by Rubin, 1947). It should be noted, also, that in transuterine pneumoperitoneum (Petersen), for visualizing intrapelvic organs on an *x*-ray film, it is customary to introduce as much as 1,000 ml. of carbon dioxide into the abdominal cavity; this procedure causes only moderate discomfort.

Air Embolism

Experimentally, air embolism has been studied by several investigators. As early as 1667, Ride produced death in cattle by blowing air under pressure into their jugular veins. Jung and Pierre (1935) reported, in their findings in experiments in dogs, that when air is injected in large quantities into the systemic veins death is due to the filling of the right side of the heart with air. Lenggenhager (1936), as a result of animal experiments with air, came to the conclusion that death is due to blocking of the pulmonary artery and arrest of the pulmonary circulation. Richardson *et al.* (1937) found that there was no constancy in the lethal amount of air required, even in individuals of the same species. They estimated that about 500 ml. of air would be required to kill a human being, basing their inferences on experimental air embolisms produced in small animals. Beauchesne, in 1818, during the removal of a neck tumour, observed the first recorded case of air embolism in the human—an effect of suction produced by negative venous pressure, as later indicated by Finn.

I have conducted numerous experiments introducing air, oxygen, and carbon dioxide into the blood streams of rabbits, with the following conclusions: if one minute is taken to inject each gas the large majority of rabbits will die almost immediately with 3 ml. of air and with 4 ml. of oxygen; most of them suffer no ill effects with 15 ml. of carbon dioxide, although larger amounts can be fatal. A fatal effect from carbon dioxide can also be produced if the rate of flow of the gas is increased—for example, 30 ml. in half a minute. Immediate necropsy of the heart of the rabbit injected with air shows the right side filled with frothy blood; examination of the brain reveals air bubbles in the capillaries. It is of interest to note that the necropsy in the cases of Moench and of Dible *et al.* showed the right auricle and ventricle to be filled with "frothy air" and, in the case of Finn, revealed "25 ml. of air in the right ventricle and pulmonary arteries."

There is therefore clear evidence on clinical, physiological, and experimental grounds that insufflation with air is potentially dangerous. It may be true, as Dible *et al.* state, that the risk of air embolism could probably be abolished in tubal insufflation if the amount of air were carefully measured and never allowed to exceed a total of 100 ml., and there is no doubt that several thousand insufflations with air have been performed without ill effect or fatality by many careful investigators all over the world. Nevertheless, the great safety of carbon dioxide makes it incontestably the gas of choice; furthermore, precision apparatus, in which the discharge of gas and the rate of flow are

accurately measured, is now widely available. Moreover, I have found no ill effect in several hundred patients in doing insufflation at the premenstrual phase of the cycle, followed a few moments later by endometrial biopsy. I have also insufflated a few patients during menstruation; but would be very unwilling to do either of these procedures with air. In fact, it is now my routine practice to perform insufflation in the premenstrual stage, and then do an endometrial biopsy in order to get, at one sitting, the three observations—patency, premenstrual changes, and unsuspected tuberculosis.

It cannot be too strongly stressed that a simple diagnostic procedure such as tubal insufflation must carry the minimal risk of ill effect, such as introduction or spread of infection, and that embolic death due to the test is a catastrophe that must never happen. I have tried to show that the risk of utero-tubal insufflation with air (or oxygen) is not negligible, and its use can no longer be justified. The first lesson may thus be briefly stated—carbon dioxide is unquestionably the gas of choice, and its risks are trivial.

Criteria of Tubal Blockage

The second lesson that I have learned concerns the criterion or criteria, on insufflation grounds only, of tubal blockage. For many years it has been widely accepted that a "negative insufflation" means that gas fails to pass at 200 mm. Hg (the usual upper limit) and that this implies tubal blockage. In the course of numerous tests, using 250 mm. Hg as the upper limit, I have often found that gas has passed between the 200 and 250 mm. limits. I have not encountered any ill effects or sequelae since adopting as a routine the pressure of 250 mm. Hg as the upper limit. Moreover, insufflation experiments using high pressures have been conducted in the course of abdominal operations for tubal sterilization or salpingostomy. In two cases of tubal blockage (tuberculous) a sustained pressure of 250 mm. Hg made no apparent impression on the tubes, and in another similar case the finding was the same with a pressure of 320 mm. Hg. There can be little doubt that a pressure of 250 mm. Hg is safe and that greater accuracy of results would be obtained if the routine upper limit of pressure were raised to this figure. But a single finding of apparent non-patency, even at 250 mm. Hg, is not necessarily indicative of tubal occlusion. This has been proved by the subsequent occurrence of a characteristic kymographic tracing of patency (corroborated by the demonstration of pneumoperitoneum or, in the non-anaesthetized, by shoulder pain), or by hysterosalpingography, or by the occurrence of pregnancy.

In a consecutive series of 102 patients in whom the tubes were not permeable to gas on insufflation under anaesthesia, and in whom dilatation of the cervix and endometrial biopsy were thereupon performed, repetition of the test a few days later without anaesthesia showed normal patency in 70 (69%). This would indicate that only 31% of these cases showing non-patency on a single test actually have occluded tubes. A similar finding is obtained in the anaesthetized patient if, after a negative result, the cervix is dilated to permit the introduction of a Bonney intrauterine cannula and a second insufflation is then done. Some investigators report that after one negative test they repeat it, having previously administered a sedative or an antispasmodic. They then attribute any successes to the drug. Marsálek and Zenísek (1952), however, conducted trials in 73 cases with various spasmolytic drugs (atropine, papaverine, novopon, morphine, contraspan, nitroglycerin) given before tubal insufflation, and concluded that these drugs increased muscular tone and amplitude—that is, had an effect rather opposite to spasmolysis. Admittedly, tubal spasm seems to be a frequent cause of fallacious negative findings; indeed, the purpose of cervical dilatation in these cases is to resolve this spasm.

On the other hand, as stated above, I have seen many tubes apparently non-patent under reasonably deep anaesthesia that later proved permeable to gas without premedication. The lesson is therefore that an insufflation finding of non-patency at 200 mm. Hg does not necessarily connote tubal occlusion, and that two or more tests, with the pressure advanced to 250 mm. Hg if necessary, are more likely to provide a reliable diagnosis. In the event of a negative finding in an anaesthetized patient, the cervix should be dilated and insufflation again performed. Great care should be taken before concluding that tubes are non-patent: this may be apparent and not real. If the first negative finding is obtained under anaesthesia, a second test should be performed without anaesthesia. In all cases diagnosed as non-patent, a hysterosalpingogram should be made. This is unlikely to correct the diagnosis but will provide a strong corroboration of non-patency and will usually help to demonstrate the site of occlusion.

Therapeutic Possibilities of Insufflation

The third lesson concerns the therapeutic possibilities of insufflation which have often been stressed. Many observers have recorded pregnancies following very soon after the test. The possibility, however, of chance or coincidence cannot be dismissed, and precise statistical assessment of results would be difficult. Other procedures possessing the common factor of instrumentation of the cervical canal, such as dilatation of the cervix (first advocated by MacIntosh, of Edinburgh, in 1826) and hysterosalpingography, have been known for many years to be followed frequently by pregnancy. The *modus operandi* of cure by insufflation has been discussed at length by Rubin, 1947), who believes it to be due to one or more of the following effects: (1) establishing patency of the genital tract; (2) removal of the cervical mucous plug; (3) dilatation of the tubes; and (4) possible psychic effect.

In an attempt to assess the "cervical-instrumentation factor," some six years ago I began a study of a consecutive unselected series of infertile women, in whom nothing more was done than the mere passing of a uterine sound. Three hundred patients were so treated and followed up. Of 253 patients traced, 45 (17.7%) became pregnant within 12 months after the sound was passed. This "sound" group warrants comparison with an insufflation series (Sharman, 1950), on the grounds of being unselected and of being statistically similar in respect of age distribution and duration of marriage. In the insufflation series of 902 patients with primary sterility, 271 (30%) became pregnant within 12 months. In my experience, therefore, the therapeutic effect of insufflation is much greater than that of the passing of a uterine sound. Rubin (1953) summarized the situation recently in declaring that the value of insufflation in tubal occlusion encountered in hydrosalpinx, or clubbed fimbrial ends, or atresia of the tubal lumen is purely diagnostic, but that, after subjecting data to the strictest criteria, it seems justifiable to conclude that the procedure exerts a therapeutic effect in sterile women whose Fallopian tubes obstruct the ovum.

The Kymograph as an Adjunct

The fourth lesson concerns the value of the addition of a kymograph to insufflation apparatus. In my opinion it is a valuable adjunct, and anyone who once uses it is reluctant to abandon it. The value of the kymograph is that it serves to distinguish not only between patent and non-patent tubes but also between tubes which are normally patent and those which are the site of spasm, stenosis, or peritubal adhesions. It is more accurate than the older types of insufflation apparatus, it gives a permanent record of the tests and their results, and it enables the results of tests on different dates to be compared. As a mere vehicle for passing gas into the tubes it has few, if any, advantages over the older types of apparatus; but in so far as it allows more accurate diagnosis it promotes rational treatment.

It may be asked whether the extra information gained by kymographic methods is worth the inevitable elaboration of the apparatus and the slightly increased trouble to the investigator. The reply to this is: modern apparatus has more than compensated for being elaborate by being simple

to operate. No great difference, either in the level at which patency is established or in the appearance of tubal-contraction waves, is usually seen when insufflation is repeated even after several months. Rubin (1939) maintains that the tracings can be correlated with phases of endometrial or ovarian activity. I have not been able to confirm this. More active or more frequent peristalsis may be seen at various stages of the menstrual cycle and spasm may also be exhibited for no apparent reason. Moreover, if two or three insufflations are performed on the one day—that is, within a few hours of one another—the tracings obtained need not be closely similar.

Summary

Some of the more important lessons gained from just over 4,000 utero-tubal insufflations during the past 25 years are:

(1) Practice bears out the theoretical advantages of carbon dioxide. There were only five cases of infection and no deaths.

(2) Two or more tests, with the pressure advanced to 250 mm. Hg, one at least without anaesthesia, provide a reliable diagnosis of non-patency.

(3) Primary sterility patients numbering 902 were traced for 12 months; 30% became pregnant. In a group of 253 patients in whom a uterine sound was passed, only 17.7% became pregnant within twelve months.

(4) The kymograph is a useful adjunct.

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"Arterial Grafting" was the subject of a meeting of the Section of Surgery of the Manchester Medical Society at which Professor C. G. Rob spoke on December 12, 1953. He began by outlining the history of the subject. In 1912 Carrel had been awarded the Nobel Prize for his researches on blood vessel grafting and the transplantation of tissues and organs; in 1913 Lexer reported that he had resected three aneurysms of peripheral arteries and restored continuity with an autogenous vein graft. The first successful arterial graft in man was inserted by Gross in 1947; he established an artery bank based on the principles elaborated by Carrel. The indications for blood vessel grafting included congenital abnormalities, such as certain coarctations of the aorta, some aneurysms and arterio-venous fistulae, wounds, primary thromboses, after some emboli, occasionally in malignant disease, and in arteriosclerosis after very careful selection. Most of these indications were obvious, but the question of arterial grafting in patients with arteriosclerotic occlusion of major vessels was debatable. These patients had a general disease; the arteriogram often showed a lesion anatomically suitable for grafting, but one was treating a patient and not an arteriogram. In all Professor Rob had grafted 35 arteries, but had treated in this way less than 3% of patients with arteriosclerosis who presented with the complaint of intermittent claudication.

DIAGNOSIS AND TREATMENT OF GALACTOSAEMIA

BY

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Galactose, formed during the metabolism of lactose, is normally converted into glycogen in the liver. In the condition known as galactosaemia this process is defective, resulting in a high concentration of galactose in the blood and its excretion in the urine. It is probable that galactose in such concentrations is toxic to some tissues and is itself responsible for the main pathological changes, but the exact pathogenesis is still uncertain. This disease is of more than academic interest because prompt treatment may bring excellent results. The original clinical description was by von Reuss (1908). Göppert (1917) was the first to report a familial incidence. Articles on the subject have appeared with increasing frequency in the past seven years, mainly in American paediatric journals. Gorter (1951) gave an account of the disease at a meeting of the British Paediatric Association, but no cases were reported in this country until Bray, Isaac, and Watkins (1952) published three and gave a full review of the literature. We know of other cases that have been diagnosed in this country, but we feel sure that knowledge of the disease is not yet widespread enough. An increased awareness will lead to earlier and more frequent detection of the disease.

The earliest signs appear in the neonatal period. The infant is reluctant to feed, may vomit occasionally, and is slow to gain weight. Jaundice is common but varies in intensity. In the most severe cases deep jaundice and ascites develop in 4 to 5 weeks and the infant dies from hepatic failure. In milder cases the infants pass gradually into a state of marasmus, and at 6 months may be only a few ounces over their birth weight. Enlargement of the liver is a constant physical finding, the edge being firm and extending nearly to the umbilicus. The spleen may be palpable. Lamellar cataracts are often found, but are not easy to detect in the early stages. Mental retardation is usually obvious by the end of the first year. Early routine investigations should reveal albumin and a reducing substance in the urine. The latter must be identified as galactose to establish the diagnosis.

Basically the treatment consists in removing lactose from the diet. When this is done rapid improvement may follow. The appetite returns, the weight increases, and the liver edge gradually recedes. Galactose disappears from the urine in one to two days and albumin a few days later. Cataracts may disappear in cases in which treatment is started early, in others needling may be necessary. Mental impairment has persisted in many

published cases, but further observation is needed to show whether early treatment will prevent this. The galactose-tolerance test is likely to remain permanently abnormal. Two patients at the ages of 18 years (Townsend, Mason, and Strong, 1951) and 7 years (Bray, Isaac, and Watkins, 1952) have been able to take some lactose in the diet without excreting galactose in the urine. Experience of the disease is still too limited for an accurate assessment of the prognosis following treatment. Reports of four recent cases are given below.

Case 1

A full-term male infant weighing 7 lb. (3,175 g.) was born on February 2, 1952. Two siblings were said to have died from pneumonia, one at 3 months and the other at 11 months. It was not possible to obtain information from the mother on the question of consanguinity.

FIG. 1.—Case 1 on admission, aged 3 months.

Early feeding difficulties and poor home conditions necessitated several admissions to hospital and then to a residential nursery. When 3 months old he was transferred to Whiston County Hospital under the care of one of us (R. H. W.-J.). Because of the disproportionate size of his head to his wasted body he was sent in with a provisional diagnosis of hydrocephalus. His weight was 8 lb. (3,630 g.) and his head circumference 15 in. (38 cm.). He was emaciated and miserable (Fig. 1). His heart and lungs were normal; his liver was enlarged, the edge being firm and palpable four fingerbreadths below the costal margin. Because of a wide and rather tense fontanelle a lumbar puncture was performed. The sugar content of the C.S.F. was 222 mg. per 100 ml. (as glucose), the other constituents being normal. This was the first clue to the correct diagnosis. The urine contained albumin but no casts. A reducing substance was present. The latter was thought to be galactose because mucic acid crystals were formed and Tollen's test was negative for pentose and glycuronic acid but positive for galactose. The fasting blood sugar was 190 mg. per 100 ml. (as glucose), and the glucose-tolerance curve was abnormal, rising to 285 mg. after one hour. A paper chromatogram of the urine before starting treatment showed a normal amino-acid pattern.

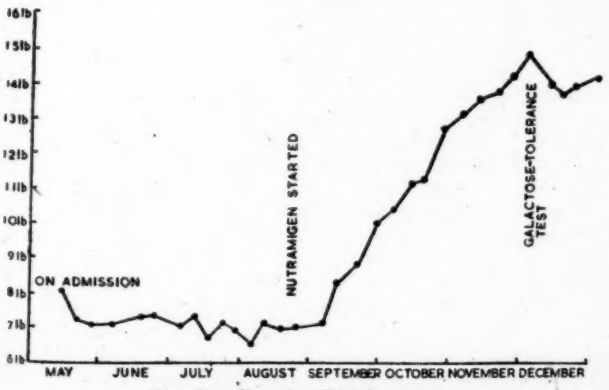

FIG. 2.—Case 1. Weight curve.

The mother's Wassermann reaction was negative. The patient's Wassermann reaction was negative; blood urea, 47 mg. per 100 ml.; haemoglobin, 8.9 g. per 100 ml.; thymol turbidity, 3 units; alkaline phosphatase, 6.6 units per 100 ml. serum (King-Armstrong). *X*-ray films of the skull and long bones showed slight generalized osteoporosis. Mr. J. M. Broderick (ophthalmic surgeon) reported fine but distinct lineal opacities towards the periphery of each lens which were thought to be early lamellar cataracts.

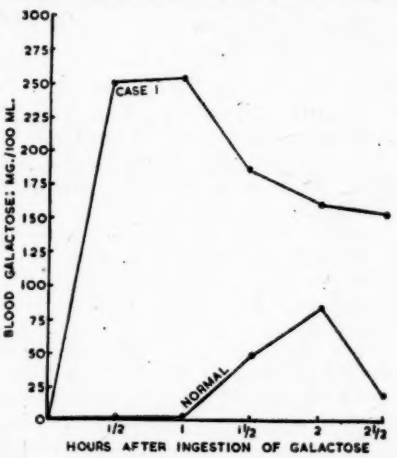

FIG. 3.—Case 1. Galactose-tolerance curves (1.75 g. galactose per kg. body weight).

From the time of admission the baby was reluctant to take feeds of dried milk and sometimes vomited. In the first week he lost 1 lb. (454 g.) in weight. A formula containing lactose-free protein, "dextri-maltose," and fat was given, but this was persistently refused and it was necessary to return to unmodified dried milk. When "nutramigen" was obtained the effect was dramatic. From the first feed the baby took well, and the weight, which had remained at about 7 lb., began to rise steeply and continued to do so (Fig. 2). The liver gradually returned to normal size, the cataracts disappeared, and the urine remained free from reducing substances. A galactose-tolerance test (Fig. 3) was performed when the baby weighed 15 lb. (6,800 g.). This helped to confirm the diagnosis, but for two weeks afterwards he was apathetic and listless, and lost weight. When 11 months old his condition had greatly improved (Fig. 4); he could raise his head from the pillow, smile, recognize people, and play with a rattle. He continued to take nutramigen well, and later had a lactose-free mixed diet.

Case 2

This infant, the first baby of healthy and unrelated parents, was born in 1949. She weighed 6 lb. 8 oz. (2,948 g.) at birth, and was delivered spontaneously after an uneventful pregnancy which went to term. Slight jaundice was present on the sixth day. It was deeper on the ninth day, and as she was feeding badly she was admitted to Alder Hey Children's Hospital. She was afebrile, the um-

FIG. 4.—Case 1 aged 8 months.

bilicus was slightly infected, and there was oral thrush. The liver was felt one fingerbreadth below the rib margin. A few days later there was severe haemorrhage from the umbilicus; the jaundice was deeper and the liver larger. Her urine contained albumin and bile, but there is no record that it was ever tested for reducing substances. The Wassermann reaction was negative and there was no evidence of haemolytic disease of the newborn. The presumptive diagnosis was septicaemia and hepatitis due to umbilical infection. Treatment with penicillin and streptomycin had no effect, and she died 46 days after birth.

Case 3

A sister of Case 2 was born in 1952, after an uneventful pregnancy which went to term. She had a healthy brother, born in 1950. Her birth weight was 6 lb. (2,720 g.). Jaundice was noticed when she was 5 days old; it became deeper and she was admitted to Alder Hey Children's Hospital on the tenth day. She was then a vigorous infant ½ lb. (227 g.) below her birth weight. There was deep jaundice, and a little blood-stained discharge from the umbilicus. The liver edge was firm and reached 1 in. (2.5 cm.) below the costal margin. Breast-feeding was continued after admission. The provisional diagnosis was congenital familial cirrhosis of the liver, but antibiotics were given because of umbilical sepsis. Four days after admission, when jaundice was deeper and the infant was lethargic and feeding badly, a reducing substance was found in the urine. Very early lamellar cataracts were then discovered. Laboratory investigations at this stage gave the following results:—Urine: a large amount of albumin, bile salts, and pigments present; acetone absent; a reducing non-fermentable sugar present, confirmed as galactose by paper chromatography. Faeces: bilirubin present. Serum: thymol turbidity, 1.3 units; thymol flocculation negative; colloidal gold, 0; alkaline phosphatase, 46.5 K.-A. units per 100 ml.; bilirubin, 23.6 mg. per 100 ml. Blood: Wassermann reaction negative; group O Rh positive (mother: group A Rh positive); sugar, 230 mg. per 100 ml. (as glucose), 200 mg. per 100 ml. being a non-fermentable sugar.

As soon as galactosaemia was suspected breast-feeding was stopped and 5% glucose-saline with added "casinal" (a calcium salt of casein, 90% protein) was given by bottle. After six days she had gained 9 oz. (255 g.) in weight and her appetite and vigour had improved, her liver was smaller and the jaundice was less. Investigations now showed the urine to contain a little albumin but no galactose; blood sugar, 95 mg. per 100 ml.; serum: thymol turbidity, 0; alkaline phosphatase, 11.5 K.-A. units per 100 ml.; bilirubin, 8.6 mg. per 100 ml. A lactose-free peptone was then substituted for the casinal and a few days later a little emulsified butter was added to the feed. Sixteen days after admission she developed a respiratory infection and diarrhoea. She became extremely acidotic and failed to respond to antibiotics and intravenous therapy, dying when 26 days old. Subsequent investigations of earlier specimens of urine showed gross aminoaciduria and, though this persisted, it was definitely weaker in specimens collected after eighteen days of treatment.

Case 4

The second child of healthy unrelated parents was born at term after an uneventful pregnancy. The first child was 7 years old and healthy. The patient's birth weight was 7 lb. 6 oz. (3,245 g.). She was breast-fed for two weeks, then given dried milk. There was mild jaundice from the fifth to the ninth days. She appeared well until the twenty-third day, when she became drowsy and was reluctant to feed. She was admitted to Alder Hey Children's Hospital the next day. Her temperature was normal but she looked very ill. Her abdomen was distended, free fluid was present, and the liver was moderately enlarged. She died 12 hours after admission. Lumbar puncture was performed soon after admission; the turbid fluid obtained yielded a growth of *Str. pneumoniae*. The total sugar was 280 mg. per 100 ml., of which 210 mg. per 100 ml. was non-fermentable sugar. Chromatography confirmed the presence of galactose.

Post-mortem Findings

The following is a brief summary of the pathological findings; a detailed report will be published elsewhere (B. G. Ockenden).

In all three cases the livers were enlarged, firm, and dark green in colour, with finely granular or wrinkled surfaces. Histological examination showed a uniform diffuse fibrosis, mainly periportal, proliferation of the smaller bile ducts, loss of the normal liver pattern, and an alveolar arrangement of the liver cells. In the two untreated cases the liver cells were vacuolated and contained lipoid; in the treated case only traces of fat were present.

The kidneys of Case 2 were enlarged. Those of Cases 3 and 4 were of normal size and showed no macroscopic abnormality, but histological examination showed marked dilatation of the proximal convoluted tubules.

Final Pathological Diagnoses.—Case 2: A diagnosis of cirrhosis of the liver of unknown aetiology was made until 1952, when a sibling (Case 3) was found to have galactosaemia. Despite the complete lack of biochemical evidence, the similarity of the gross and microscopical findings in the liver was such that we are certain that this was also a case of galactosaemia. *Case 3:* Acidosis and uraemia; haemorrhagic bronchopneumonia; galactosaemia; cirrhosis of the liver. *Case 4:* Pneumococcal peritonitis and septicaemia; galactosaemia; cirrhosis of the liver.

Discussion

Diagnosis

The diagnosis has often been missed or long delayed simply because the urine has not been tested for sugar, or if a reducing substance has been found its significance has not been appreciated. It is not always easy to obtain a sample of urine from an infant, but the importance of early treatment in galactosaemia makes the omission inexcusable when investigating neonatal jaundice, marasmus, and hepatomegaly. Once melituria and hyperglycaemia have been confirmed rapid identification of galactose must follow. Fermentation tests applied to both urine and blood should show that the reducing substance in the former and a high proportion of it in the latter are non-fermentable. It should be borne in mind, however, that some samples of yeast do ferment galactose.

Until the advent of chromatography the identification of this non-fermentable reducing substance as galactose depended on chemical tests. Some of these—for example, Barfoed's test (for monosaccharides), mucic acid production (lactose or galactose), and Bial's test (to exclude pentosuria)—may work well enough when sufficient reducing substance is present, but others—for example, osazone production—give inconclusive results when applied to relatively small amounts of complex biological fluids. Paper chromatography used in conjunction with the fermentation methods will give an answer overnight with a high degree of accuracy. Galactose is easily distinguished from three of the other sugars most likely to be found in urine (pentose, lactose, and fructose), either by differences in rate of movement or by the use of selected spraying agents. The distinction from glucose, however, is not so easy. Glucose and galactose have similar rates of movement in butanol-acetic-acid mixture and other common solvents used for sugar chromatography. The only distinguishing feature between them brought out by spraying agents is by the use of phloroglucinol when galactose turns a faint brown and glucose remains colourless. Three-day runs in butanol-acetic-acid mixture are reported to give sufficient separation. For rapid (overnight) identification it is best to make two separate runs in different solvents—for example, butanol-acetic-acid mixture and *p*-cresol; in the former the glucose spot (rf 0.19) runs a shade further than the galactose one (rf 0.17); in the latter solvent the positions are reversed.

Secondary biochemical investigations are concentrated on the detection and assessment of possible liver damage. These involve the usual liver-function tests—for example, examination for bile pigments in urine and faeces, estima-

tion of serum bilirubin and alkaline phosphatase, flocculation tests, etc. A galactose-tolerance test helps in diagnosis, but its performance is not without danger. When the blood galactose rises there may be a brief but serious fall in blood glucose, while the galactose deliberately given may aggravate the symptoms of the disease, as occurred in Case 1.

Gross aminoaciduria is usually detectable in untreated cases of galactosaemia, and here again chromatography is of great value. Amino-acids were not found, however, in Case 1, even before treatment was started. In Case 3 16 or more amino-acids were present, including cystine, tyrosine, aspartic acid, glutamine, serine, glycine, lysine, taurine, alanine, threonine, and possibly citrulline. The total amino-acid nitrogen in the blood was 4.8 mg. per 100 ml. In cases reported by Holzel *et al.* (1952) there was less aminoaciduria after treatment, but Bickel and Hickmans (1952) found it undiminished after a period on a lactose-free diet.

In Case 4 galactosaemia was not suspected until sections of the liver were examined. Only 2 ml. of C.S.F. was then available, but this proved sufficient to confirm the diagnosis; chemical estimation showed a high percentage of non-fermentable sugar confirmed as galactose by paper chromatography.

Treatment

The essential treatment is to remove lactose from the diet. It is not easy to provide a suitable substitute for whole milk for an infant. Case 1 was first offered a formula containing "pronutrin" (an enzymatic hydrolysate of casein), dextri-maltose, brewer's yeast, and water, and later this was replaced by lactose-free peptone, dextri-maltose, cod-liver oil, and water. Both feeds were often refused and had to be abandoned, presumably because they were not palatable. In cases reported by DuShane and Hartman (1951) and by Townsend, Mason, and Strong (1951), a soya bean formula was tried but not tolerated. Goldbloom and Brickman (1946) found such a formula suitable for one baby but not for another. In a number of other cases in which the outcome was satisfactory, nutramigen was used. This preparation consists of dextri-maltose 45.2%, amigen 20% (a non-antigenic pancreatic digest of casein consisting of amino-acids and short-chain polypeptides), corn oil 18%, arrowroot starch 10%, calcium gluconate 3.5%, other mineral substances 3.2%, crystalline vitamins 0.6%, calories 130 to the ounce. It has to be imported from America because no lactose-free infant food is made in this country. Supplies arrived too late for Case 3, but when used for Case 1 the results were most gratifying.

It is possible that the diarrhoea which developed in Case 3 was of infective origin, but it might have been due to the metabolic disturbances of the disease and the feeding difficulties. In the early stages of treatment, particularly in the neonatal period, the infant should be in hospital, where biochemical facilities are available for the control of treatment.

The problem of avoiding lactose becomes much simpler when mixed feeding is introduced, while later in childhood small quantities may be harmless.

Inheritance

From the literature so far published it is not possible to be sure how often the disease affects siblings or what proportion of them will be involved in any one family. Retrospective inquiry often gives a history suggesting that galactosaemia has caused the death in infancy of other members of the family, but proof is impossible. The question of consanguinity of the parents is rarely mentioned. Professor L. S. Penrose (personal communication) suggests that the disease may be due to a recessive gene in homozygous form. If so, the chance of a child in an affected family showing the disease would be one in four. The incidence in the family histories reported by Göppert (1917), Donnell and Lann (1951), and Gorter (1951) would, however, be higher than this, if suspected cases could have been confirmed.

ADDENDUM.—Since the paper was completed the mother of Case 1 has given birth to a girl who after six weeks has shown no reducing substances in the urine. She appears to be healthy. The mother of Cases 2 and 3 has had binovular twin boys (there were two separate placentae). The infants were breast-fed for two and a half weeks, and then took half-cream National dried milk. Samples of urine were examined daily for the first 12 days. Several specimens from each infant contained a reducing substance (up to 0.4 g.%, as glucose). Paper chromatography revealed the presence of a little galactose on four occasions. When the infants were 4 weeks old no reducing substances were found in one specimen of urine from each. Amino-acids in the urine did not differ from those to be expected in the newborn. Both infants appeared to be quite healthy and were gaining weight very well when 6 weeks old.

We wish to thank Dr. R. M. Todd for permission to include Case 4; Dr. F. Fletcher, of Bengers Ltd., for a supply of lactose-free peptone; Dr. C. E. Dent for confirming the aminoaciduria in Case 3; and Dr. R. W. Brookfield and Dr. E. G. Hall for criticism and advice.

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GALACTOSE DIABETES

BY

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Galactose diabetes is a rare inborn error of galactose metabolism. Although originally described by von Reuss in 1908, the condition does not seem to have been reported in this country until Holzel and others (1952) described two cases associated with aminoaciduria.

The essential features of the disease are failure to thrive dating from the neonatal period, hepatomegaly, albuminuria, and galactosuria. In addition, the serum bilirubin is commonly elevated and jaundice may even be detected clinically. The liver-function tests may be abnormal. Nuclear cataracts sometimes occur and mental deficiency may appear in those surviving infancy. Occasionally the disease is familial.

In the case here described bouts of remittent pyrexia occurred, the duration of the fever varying from two to seven days. On two occasions there was an associated upper respiratory infection, but on the other six occasions no satisfactory explanation of the pyrexia could be found. Blood cultures were repeatedly negative and there was no response to sulphonamide, penicillin, or aureomycin therapy. Similar periods of pyrexia have been mentioned in previous case reports, and they would seem to form an integral part of the syndrome.

Treatment consists in the exclusion of galactose from the diet, and this is achieved in infancy by feeding a lactose-free milk substitute. If this therapy is instituted early, the manifestations of the disease are largely reversible, but if diagnosis is delayed the prognosis is poor.

Case Report

A male infant aged 4 months was admitted to hospital on August 30, 1951, because of failure to thrive. He was born at term, weighing 7 lb. 10 oz. (3.5 kg.). The labour was normal. His mother thought that he was a little jaundiced for a few days after birth. Breast feeding was not attempted and the baby was fed on a proprietary food until admission to hospital. Although he took his feeds eagerly and neither vomited nor had diarrhoea, he did not thrive prior to admission to hospital. His mother, father, and brother aged 4 years were stated to be in good health. The brother was examined clinically and no abnormality was detected.

On admission the infant did not look ill but was obviously underweight. His weight was 8 lb. 9 oz. (3.9 kg.), temperature 98° F. (36.7° C.), pulse 146, and respirations 30. On clinical examination the only abnormality was a firm enlargement of the liver to three fingerbreadths below the costal margin. The haemoglobin was 80% Sahli, the white blood cells numbered 21,000 per c.mm., and his blood was group O Rh-positive. The mother's blood was group O Rh-positive. On chemical examination of the urine no albumin or sugar was detected and microscopically no white blood cells or red blood cells were seen. Urine culture gave a light growth of *Streptococcus faecalis* and *Bact. coli*. The stools appeared to be normal, and on culture no pathogens were obtained. The Mantoux reaction (1 : 1,000) was negative. The Wassermann reaction was negative.

The infant fed well on full-cream National dried milk, but did not gain weight. Throughout the course of his illness bouts of pyrexia, as described above, occurred. The urine was repeatedly found to be normal, both chemically and microscopically, until the 35th day after admission, when a trace of albumin was detected. This albuminuria persisted, and on the 46th day Benedict's test became positive. Further laboratory investigation (see below) showed this reducing substance to be galactose. On the 97th day the infant was put on a lactose-free soya-flour mixture, which he took well. This resulted in the urine becoming sugar-free within 48 hours. He started to gain weight and his general condition improved, although there was no change in the size of his liver. A return to milk feeding for 24 hours resulted in the reappearance of a positive Benedict's test and the development of slight pitting oedema. However, these both disappeared when a lactose-free diet was recommenced. On the 147th day he developed an upper respiratory infection with pyrexia, vomiting, and diarrhoea. Chloramphenicol therapy was instituted. His condition appeared to be improving, when on the 156th day he collapsed suddenly after a feed and died within a few seconds.

Biochemical Investigations

Urine.—Chemical and microscopical examinations for cystine were negative on four occasions (October 17 and 25, and November 2 and 19). Amino-acid nitrogen on October 17, 23, and 31, and November 2 and 19 was 60, 116, 35, 40, and 30 mg. per 100 ml. respectively.

Blood.—September 6: serum proteins, 5.5 g. per 100 ml.; serum albumin, 4.2 g. per 100 ml.; serum globulin, 1.3 g. per 100 ml.; serum bilirubin, 0.5 mg. per 100 ml.; serum alkaline phosphatase, 42.1 units per 100 ml.; thymol turbidity, 3 units. October 16: blood urea, 31 mg. per 100 ml.; blood cholesterol, 140 mg. per 100 ml. October 17: serum alkaline phosphatase, 23.5 units per 100 ml. October 26: serum proteins, 6.25 g. per 100 ml.; serum albumin, 4 g. per 100 ml.; serum globulin, 2.25 g. per 100 ml.; serum bilirubin, 1.4 mg. per 100 ml.; serum alkaline phosphatase, 15 units per 100 ml.; thymol turbidity, 3 units. November 9: blood-sugar curve after 20 g. glucose orally was: fasting specimen, 110 mg.; ½ hour after 20 g. of glucose orally, 194 mg.; 1 hour after, 206 mg.; 1½ hours after, 183 mg.; 2 hours after, 181 mg. per 100 ml. (Further investigations were planned—for example, galactose-tolerance test—but owing to the clinical condition of the patient these were not carried out.)

Identification of the Reducing Substance in the Urine.—The reducing substance present was provisionally identified as galactose on the following grounds; it was not fermented by yeast; Bial's test for pentose was negative; Tollens's phloroglucinol test was positive on prolonged boiling, as with pure galactose. The osazone was identical in crystalline form and in melting-point with that prepared from galactose. No depression of melting-point was produced on mixing the osazone isolated from the urine with known galactosazone. Mr. A. P. Kenny kindly confirmed the identification of the reducing substance in the urine by means of paper partition chromatography. He reported that the conclusion to be drawn from the chromatograms was that the principal reducing sugar in the urine was galactose, with a possible trace of free amino-sugar in certain specimens.

Aminoaciduria.—In no specimen of urine was the gross aminoaciduria recorded by Holzel *et al.* observed. Dr. H. Ellis C. Wilson kindly carried out two-way paper chromatograms of the urinary amino-acids. No gross aminoaciduria was observed. The following amino-acids were identified: glutamic acid, glycine, threonine, glutamine, alanine, phenylalanine, valine, histidine, oxyproline and nephrosis peptide.

Post-mortem Examination

The liver was regularly enlarged and of normal contour. On section there was marked pallor of the parenchyma with blurring of the lobular markings in places, giving a homogeneous appearance to the liver tissue. The lungs showed superficial areas of collapse in both lower lobes and there was congestion of all lobes, most marked basally. There was also marked pallor of the renal parenchyma and of the bowel mucosa.

Histology

The liver showed a diffuse monolobular cirrhosis with early fibrosis, formation of new bile ducts, and round-cell infiltration in the portal tracts. A few foci of round cells were seen among the liver cells. There was no glycogen present in the sections of liver examined. The ileum showed congestion of Peyer's patches with some lymphoid hyperplasia and slight round-cell infiltration in the villi. The mesenteric glands showed sinus hyperplasia. The spleen showed congestion of the pulp with reticulo-endothelial hyperplasia.

Discussion

Portal cirrhosis is a recognized complication of galactose diabetes, and although several theories have been advanced to explain its occurence none has gained general acceptance. One theory is that the portal cirrhosis is due to galactose being directly toxic to the liver; another that it results from the absolute or relative hypoglucosaemia which accompanies galactosaemia; while a third suggests that an inadequate diet leads to a deficiency of lipotrophic substances.

The discovery by Holzel *et al.* of aminoaciduria in two patients suffering from galactose diabetes suggested a further possible explanation—namely, that a deficiency of lipotrophic substances results from an excessive urinary loss of these. Such a mechanism has previously been suggested by Himsworth (1950) to explain the cirrhosis of the liver present in hepato-lenticular degeneration and Fanconi's syndrome, in both of which aminoaciduria occurs.

In the present case cirrhosis of the liver developed, although there was no gross aminoaciduria. However, the work of Bickel and Hickmans (1952) suggests that some of the amino-acids found do not occur in normal urine.

Summary

A case of galactose diabetes complicated by cirrhosis of the liver is described. The biochemical investigations are detailed with special reference to the identification of galactose in the urine and to the detection of the amino-acids in the urine. The pathogenesis of the cirrhosis of the liver is discussed.

We are indebted to Dr. J. B. McMillan, of Stobhill Hospital, Glasgow, for the pathological report; and to Dr. H. Ellis C.

Wilson, Royal Hospital for Sick Children, Glasgow, and Mr. A. P. Kenny, Victoria Infirmary, Glasgow, for undertaking the chromatography.

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ACRODYNIA ASSOCIATED WITH EXCESSIVE INTAKE OF MERCURY

BY

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Acrodynia is a disease of comparatively recent recognition, being first described in detail by Swift (1914) in Australia, and not reported in England before 1922. Since these earlier descriptions the disease has been recognized with increasing frequency in Europe and America as well as Australia, and in England it appears to be particularly prevalent in the neighbourhood of large industrial towns and cities of the North and Midlands—a distribution which may be of some significance, as is shown later. Another feature of some possible significance is the rather unusual fact that this disease is exceptional in that it affects breast-fed just as readily as artificially fed infants.

It being accepted that the cause and pathogenesis of acrodynia are unknown, it is not surprising that there have arisen a number of theories as to its origin, none of which is proved or even generally accepted. Warkany and Hubbard (1948) recorded several cases in which they suggested that the cause might be chronic metallic poisoning, incriminating mercury, and, in particular, the mercury administered so often to infants in the form of teething powders.

Bivings (1949) summarized all the recorded cases of acrodynia and found that mercury had been present in the urine of 28 out of 31 patients examined. He recorded also that of 15 patients treated with dimercaprol at least 11 showed prompt improvement or recovery; that is to say, these patients responded to the accepted treatment for mercurial poisoning.

There have been other brief references to the association of acrodynia with high levels of mercury in the urine, notably by Gaisford (1949), who states that in Manchester, where the condition is common, there is in almost every case a history of the ingestion of mercury, usually as calomel in teething powders. He states later (1950) that the general consensus of opinion appears to be that acrodynia is a general reaction to some poison in an infant hypersensitive to the offending substance, in most cases mercury. This opinion has been made widely known to chemists, being quoted in full in the *Extra Pharmacopoeia*, 1952.

Wilson, Thomson, and Holzel (1952), in describing five cases of nephrosis due to mercurial ingestion, urged that mercurial compounds should be eliminated from all teething powders, and that other mercurial compounds, such as grey pills, be used with care, and prolonged administration be avoided in young children. Less than a month later Holzel and James (1952) described 176 cases of acrodynia, over 50% of which gave a history of ingestion of teething powders, whereas of 1,561 healthy infants in the same area only 109, or 6.9%, were habitually given these powders.

Despite these numerous warnings of the potential danger of the administration of calomel to young infants, Miss Hornsby-Smith, replying on behalf of the Minister of Health to a question in the House of Commons in April, 1952, stated: "Inquiries are already in progress at various children's hospitals. Although indiscriminate use of teething powders is clearly undesirable, there is not yet definite evidence to justify general publicity."

Twenty months after that statement it does not appear that the results of the inquiries to which she referred have been made public, nor does it appear that physicians in general as yet regard the theory of Warkany and Hubbard as having been fully substantiated; for no concerted effort seems to have been directed towards the elimination of mercury from teething powders, or even towards the education of the public in the possible harmful results that may follow their administration.

The experience gained from a study of this disease in one of the industrial areas of the North Midlands, where acrodynia is particularly common, emphasizes the need for such action.

Case 1

A male child aged 9 months was seen at his home on August 6, 1952, because he was showing increasing irritability and loss of appetite. He had photophobia, was restless and miserable, sweating, had lost weight, and his hands and feet were puffy and peeling. He had marked tachycardia, and a slight sweat-rash was seen about the trunk—in fact, he presented the typical picture of acrodynia. He had been given teething powders on alternate days for the preceding three months.

On admission to hospital his urine was found to contain 1,450 μg. of mercury per litre. *X*-ray examination showed that his chest was free from disease and his Mantoux reaction was negative.

Treatment with dimercaprol was begun: 34 mg. for the first dose, followed by 17 mg. four hours later, and 17 mg. twice daily for a further two days. Ephedrine sulphate, 25 mg., was given orally before each injection.

By the fourth day after the starting of treatment the child seemed much happier, and the photophobia was less. After this course of treatment the urinary mercury dropped to 860 μg. per litre. A further course was given, using the same dosage of dimercaprol, following which his urinary mercury dropped to 300 μg. per litre.

At this stage the child became feverish, although his general condition was vastly improved, and an *x*-ray film showed an opacity in the right upper lobe. This took several weeks to resolve, not responding to antibiotics at all. At the same time radiographs of his long bones showed no abnormality; his serum calcium was 10 mg. and phosphorus 4.3 mg. per 100 ml.

A month later *x*-ray examination showed extensive decalcification of the long bones. As a result of this he was given "sterogyl," 300,000 units monthly, with calcium and phosphates by mouth daily, and it was decided not to give a further course of treatment with dimercaprol. A series of *x*-ray examinations showed that the decalcification had been arrested. Some six months from his admission to hospital his urinary mercury was down to 90 μg. per litre, his skeleton presented normal radiological appearances, and his general condition was satisfactory.

Case 2

A male child aged 10 months was admitted to hospital presenting the typical picture of acrodynia, except for the absence of any photophobia, and with a history of having been given teething powders on alternate days for a period

of nearly three months. On admission his urinary mercury amounted to 2,400 μg. per litre. He was given a course of treatment with dimercaprol similar to that in the previous case; as a result his urinary mercury dropped to 1,450 μg. per litre, with corresponding improvement in his appearance and behaviour. A second course of treatment brought the urinary mercury down to 480 μg. per litre, and as by that time the child was clinically very much improved no further dimercaprol was given. No decalcification was found in this case. He was seen again six months after his admission, when the urinary mercury was 30 μg. per litre.

Comment

It was natural that, following these two cases, a careful watch was kept for other examples of the association between acrodynia and mercury ingestion. Between August 6, 1952, and November 16, 1953, 13 cases of acrodynia have been observed in the children's ward of one hospital out of a total of 359 patients admitted, an incidence of 3.62%. In all 13 cases it was found that one particular brand of teething powder had been administered repeatedly over varying but considerable periods. In all 13 cases the level of mercury in the urine was high or very high.

Clinical details of all cases are not given, as, in general, they were similar to the two already described. The two following examples must be presented in greater detail, for reasons that will be abundantly clear.

Case 12

A female infant, who won first prize at a local show at the age of 6 months, was seen at her home on October 15, 1953, at the age of 9 months. She gave a history of increasing irritability and crying for some six weeks, and had lost weight considerably. She showed photophobia, her feet and hands were red and puffy yet felt cold, she was sweating, and there was pronounced tachycardia. It was difficult to ascertain with accuracy the exact number of teething powders administered, but it appeared that she had received at least 64 powders over a period of about six months. In view of her poor condition it was not considered wise to begin treatment with dimercaprol immediately after admission to hospital. Urine was collected for mercury estimation, and then she was given hexamethonium bromide, 10 mg. every six hours subcutaneously. For three or four days she seemed to be showing slight improvement, but then she developed pneumonia and died two days later.

In view of the large amount of mercury she was known to have ingested, and as a result of the experience gained from the previous cases, it was felt that this death could not be regarded as a natural one, and the facts were therefore reported to the city coroner. This action was amply justified by the report received after her death, to the effect that her urine contained 3,900 μg. of mercury per litre.

The necropsy confirmed the immediate cause of death to be capillary bronchitis with a patchy bronchopneumonia, but otherwise the naked-eye and microscopical examinations made no fresh contribution to the knowledge of this disease. Various organs were analysed at the West Midlands Forensic Science Laboratory, with the following result:

Analysis showed that the liver specimen contained 1.8 mg. of mercury per 100 g.; the kidney specimen contained 3.4 mg. of mercury per 100 g.; and the brain specimen contained 0.3 mg. of mercury per 100 g.

At the resumed inquest on December 2 this child's death was found to be from bronchopneumonia due to acrodynia resulting from chronic mercurial poisoning following overdosage with teething powders.

Case 13

A female infant aged 9 months was one of twins, and had been the stronger baby at birth. She was seen on November 16, 1953, with a six-weeks history of increasing irritability and fretfulness, loss of appetite, loss of weight, and sleeplessness. There was pronounced sweating, tachycardia, and hypotonia; the hands and feet appeared pink and puffy yet felt cold, and a slight rash was present about the trunk. She presented the typical picture of acrodynia, and a history was then obtained that a total of nine powders had been administered (later corrected to twelve powders). This baby was feverish on admission to hospital, but an *x*-ray film of her chest was clear, and it was decided, in view of the previous case, to begin treatment with dimercaprol without waiting for the result of the urinary mercury estimation.

As the child's condition was rapidly deteriorating this form of treatment was suspended the next day after only three doses, each of 17 mg., had been given. No response was obtained to treatment with chloramphenicol and she died on November 21.

At the time of this child's death the inquest on the previous case was still open, and it was felt that the only course of action was to notify this case likewise to the city coroner, although, as in the previous case, the result of the urinary mercury estimation was not known at the time of death.

At necropsy the immediate cause of death was found to be bronchopneumonia; this was confirmed on microscopical examination, when, in addition, the kidneys showed cloudy swelling and the presence of casts in the proximal set of convoluted tubules and the loops of Henle.

The urine obtained on admission to hospital was found to contain 300 μg. of mercury per litre, and a sample obtained after death contained 470 μg. The analysis of various organs at the West Midlands Forensic Science Laboratory showed the following result:

Analysis showed that the liver specimen contained 570 μg. of mercury per 100 g.; the kidney specimen contained 1,100 μg. per 100 g.; and the brain specimen contained 180 μg. per 100 g.

At the resumed inquest on December 9, 1953, death was found to be from bronchopneumonia due to acrodynia arising from chronic mercurial poisoning through teething powders "to which the child was susceptible."

An interesting feature in this case is the deceased child's surviving twin brother, who acted as a natural control. He had never been given any teething powders, remained perfectly well, and instead of 470 μg. his urine was found to contain only 25 μg. of mercury per litre. This is well within normal limits.

Discussion

While Cases 12 and 13 are very similar in the main facts, they have important differences, and Case 13 might be regarded as complementary to the first, in that it provides an answer to certain points which remained in doubt at the end of the first inquest.

In both inquests the verdict was death from pneumonia arising during the course of acrodynia due to chronic mercurial poisoning resulting from the ingestion of teething powders containing calomel. In the first case this was said to be the unfortunate result of an overdose of the powders. Indeed, because of the very large number of powders administered over such a very long period, it could not be denied that overdosage had occurred. The reports of the inquest in the daily press appeared to stress the overdosage, and probably left the impression, by inference, that some "normal" dosage was a safe one.

Any such impression should have been clearly contradicted by the second inquest a week later, in which death was found to have occurred as a result of chronic mercurial poisoning following the ingestion of only 12 powders.

At the second inquest a suggestion was made that this child had been hypersensitive to calomel—a suggestion that has found a place in the literature on more than one occasion by way of explanation for the apparently close association between acrodynia and the ingestion of calomel.

Where the state of hypersensitivity, or idiosyncrasy, to a drug exists it is to be expected that severe and unusual reactions may occur following the ingestion of very small quantities of the drug, and that, even should death result, the analysis of the organs would not necessarily show any high level of the offending substance.

In the case of calomel, certain hypersensitive reactions have been described, such as acute exanthemata, with small scarlatiniform or urticarial eruptions on the body, excepting the palms of the hands and the soles of the feet (areas in which the signs of acrodynia are most marked), abdominal pains and diarrhoea, and elevation of the temperature; or there may be an acute eczematous type of dermatitis. These symptoms usually occur within six to eight days of taking the drug, disappear within a few days, and do not affect the general health. None of these symptoms is associated with acrodynia, nor were any present in these cases, except possibly the pyrexia, which could probably be explained on other grounds. It is quite natural, however, that children will differ considerably in their degree of sensitivity to calomel, or to any other drug, and it would appear that this child, the subject of the second inquest, was certainly more sensitive to calomel than the previous one. Distinction must be made, nevertheless, between normal variations in sensitivity and the state of hypersensitivity or idiosyncrasy, and in view of the absence of any of the usual hypersensitive symptoms, and also the proved very high mercurial content of the organs, it is quite impossible to sustain any suggestion of abnormal hypersensitivity in this case.

Controversy during the first of the two inquests revolved largely around the relatively small number of cases of acrodynia, in the face of truly startling sales of teething powders; these were stated by counsel representing the manufacturers to be no fewer than 30,000,000 per annum for this one firm alone. The other argument which was brought forward in opposition to the mercurial aetiology of acrodynia was the high incidence of the disease in the North and Midlands as against the South of England, which, according to the information supplied by counsel, is by no means proportionate to the sales of that brand of powder. The *Lancet* (1953) follows a very similar line of reasoning.

It is not denied that other factors, as yet not determined, may well play a part in the aetiology of acrodynia. These unknown factors may simply act by influencing the absorption of mercury from the bowel.

It cannot, however, be denied that evidence has been steadily increasing since 1948, and from a wide diversity of sources, incriminating mercury as an important factor in the causation of acrodynia. This series of cases, culminating in two deaths in which the organs contained very large amounts of mercury, must add considerable weight to that evidence.

Apart from the close association of mercury and acrodynia, the nephrotoxic effects of inorganic salts of mercury have long been recognized, and recent papers by Wilson, Thomson, and Holzel (1952), and by Farquhar (1953) have emphasized this danger.

At the end of the second inquest it was announced by counsel representing the manufacturers of the powders concerned in both inquests that this firm has now discontinued the use of calomel in the preparation of teething powders or soothing powders. This decision to omit the calomel from one of the popular brands of teething powders having a very wide circulation must be regarded as a highly satisfactory statement. Matters should not, however, be allowed to stop there, for there remain other manufacturers who may not take the same action. The only safe solution would appear to be for calomel and other inorganic salts of mercury to be included in Schedule 1 of the Poisons List.

On December 10 last the attention of the Home Secretary was drawn to the first of these cases, and he was asked whether, in view of the evidence, action should not be taken to prohibit the use of these substances. During the course of his reply he stated that inquiries were not yet complete. Thus his reply differed little from that made on behalf of the Minister of Health 20 months earlier.

Summary

The literature is reviewed up to date concerning the association of mercury with acrodynia. Thirteen cases are added to the number so far recorded in which there was found to be a close association; this series included two deaths which were the subject of coroners' inquests. The factors concerning the aetiology of acrodynia are discussed, with special reference to the steadily increasing evidence incriminating mercury as a major factor. A plea is added for the inclusion of calomel in Schedule 1 of the Poisons List.

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CLINICAL AND CHEMICAL STUDIES IN HUMAN LACTATION*

BY

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IV. TRENDS IN MILK COMPOSITION DURING COURSE OF LACTATION

The change which occurs in the composition of milk during the course of lactation was probably the first variation in milk to be recognized. As far back as the second century A.D., Soranus of Ephesus wrote that "during the first twenty days the mother's milk is, as a rule, unfit for consumption by the child, being thick, cheesy, and difficult to digest" (quoted by Ruhräh, 1928).

The literature of the past half-century is almost unanimous that the yield rises rapidly during the first week and more slowly thereafter, that the lactose content also rises during the first week to a level which is almost constant for the rest of lactation, and that the nitrogen content falls steeply during the first few days and more slowly thereafter. There is little information about the trends of fat content, although what evidence there is suggests a rise during the first few weeks of lactation. Morrison (1952), in his comprehensive review of human milk composition, discusses the evidence for all these changes in detail.

The present data are reported because they amplify current knowledge of these trends, although they were collected with other purposes in view. The following 24-hour samples were studied. (*a*) From lying-in patients at the Aberdeen Maternity Hospital 210 samples were collected during the first two weeks of lactation. Most of those taken during the first six days were primarily intended for the examination of diurnal variation and were therefore selected so that there would be enough milk available at each feeding for a complete analysis. In order to study differences in milk composition between individuals, 150 samples were collected on the seventh day. There was a preponderance of primiparae, but the cases otherwise form an approximately random sample of maternity hospital patients. (*b*) Thirty

*Parts I, II, and III were published last week (*Journal*, January 23, p. 175).

samples of mature milk from the 21st day of lactation or later were collected from a variety of sources; two subjects were still lying-in patients of the Aberdeen Maternity Hospital on account of post-partum complications; nine were resident in the mother and baby unit of the Royal Aberdeen Hospital for Sick Children with babies requiring some medical or surgical treatment; and another nine had been admitted with some feeding difficulty. Ten subjects were unmarried and living in the Aberdeen Mother and Baby Home. From eight of these latter subjects and from three others samples were obtained on the seventh post-partum day and also later in lactation. (*c*) From five women whose infants were premature and unfit to be put to the breast samples were obtained on a number of days during the lying-in period, and, from two of these, further samples were obtained by manual expression.

Method.—The whole contents of both breasts were removed by the "humalactor" at the usual feeding-times of 6 a.m., 10 a.m., 2 p.m., 6 p.m., and 10 p.m. After the last feeding prior to the sampling period the

TABLE I.—*Samples From the First Two Weeks of Lactation, Excluding the Seventh Day*

Case No.	No. of Pregnancy	Day	Volume (ml.)	Fat (g./100 ml.)	Lactose (g./100 ml.)	Total N. (mg./100 ml.)	N.P.N. (mg./100 ml.)	Protein (g./100 ml.)
221	5	1	54	6·80	2·40	1,061	332	4·67
223	1	1	15	2·20	5·00	1,852	654	7·68
224	1	1	28	15·65	5·21	956	437	3·33
229	1	1	12	0·90	7·05	1,791	1,082	4·54
230	1	1	7	—	4·11	—	245	—
233	2	1	12	2·65	3·97	1,292	274	6·53
117	3	2	115	2·50	6·02	449	80	2·37
172	3	2	40	1·90	5·38	925	234	4·43
201	1	2	2	—	—	951	228	4·63
220	1	2	94	3·40	6·37	550	105	2·85
224	1	2	46	6·35	6·26	550	178	2·38
233	2	2	17	3·55	4·11	960	109	5·45
236	1	2	28	0·50	6·57	1,532	563	6·21
28	1	3	461	2·55	6·61	371	70	1·93
29	6	3	121	2·15	—	—	—	—
31	2	3	124	1·85	—	—	—	—
42	2	3	699	2·40	6·17	280	50	1·47
49	2	3	307	3·20	6·02	401	64	2·16
117	3	3	530	3·30	6·41	345	92	1·62
172	3	3	323	3·45	5·65	370	64	1·96
201	1	3	52	1·20	5·27	486	102	2·46
224	1	3	295	3·85	6·37	384	85	1·92
233	2	3	170	2·90	6·37	370	111	1·66
236	1	3	235	1·90	6·09	468	85	2·46
21	2	4	566	2·90	6·17	—	—	—
27	1	4	325	3·85	6·47	409	—	—
43	2	4	459	3·20	6·04	361	68	1·88
48	1	4	500	2·20	6·57	311	87	1·44
56	2	4	810	2·60	5·82	280	73	1·33
117	3	4	550	2·90	6·71	322	88	1·50
172	3	4	416	2·70	6·01	294	63	1·48
224	1	4	425	2·80	6·34	349	88	1·67
233	2	4	190	2·80	6·47	386	109	1·78
236	1	4	340	2·60	6·19	353	83	1·73
23	1	5	342	2·40	—	—	—	—
26	3	5	287	2·30	—	—	—	—
30	1	5	270	2·80	—	—	—	—
34	8	5	304	3·05	4·83	506	62	2·85
117	3	5	745	3·45	6·78	312	70	1·55
172	3	5	431	3·55	6·44	294	63	1·48
224	1	5	450	3·50	6·51	343	83	1·67
233	2	5	180	4·40	6·02	361	87	1·76
236	1	5	305	2·95	6·23	350	87	1·69
22	1	6	681	3·50	—	—	—	—
33	1	6	738	3·65	6·64	252	67	1·19
37	3	6	372	2·70	6·56	297	73	1·44
40	3	6	418	2·10	6·29	302	70	1·49
41	3	6	502	4·80	5·98	395	82	2·01
172	3	6	524	2·90	6·47	283	61	1·42
224	1	6	419	4·60	5·96	340	77	1·69
233	2	6	275	2·40	6·16	302	73	1·47
236	1	6	560	2·80	6·44	342	87	1·63
38	1	8	219	1·45	6·56	255	68	1·20
70	2	8	710	2·00	6·57	260	53	1·33
172	4	8	670	3·05	6·64	270	68	1·29
233	2	8	310	4·20	5·96	246	56	1·22
236	1	8	560	2·80	6·82	311	73	1·53
233	2	9	325	4·00	6·37	263	59	1·31
224	1	13	540	4·20	6·64	294	62	1·49
268	1	13	380	2·90	5·79	210	53	1·01

TABLE II.—*Samples From the Seventh Day of Lactation*

Case No.	No. of Pregnancy	Volume (ml.)	Fat (g./100 ml.)	Lactose (g./100 ml.)	Total N. (mg./100 ml.)	N.P.N. (mg./100 ml.)	Protein (g./100 ml.)
25	2	691	3·80	—	—	—	—
32	1	71	5·25	4·80	456	84	2·39
36	1	514	3·10	6·45	—	—	—
39	1	522	2·70	6·40	323	69	1·63
51	1	258	2·70	5·55	260	76	1·18
52	2	695	1·70	6·23	241	50	1·22
53	1	409	3·70	6·44	286	53	1·49
54	1	356	3·40	6·78	—	64	—
55	1	352	2·40	5·82	312	60	1·62
59	1	410	3·60	6·92	274	67	1·33
60	1	550	2·65	6·50	252	57	1·25
61	1	170	2·70	5·12	405	31	2·08
62	1	240	3·20	6·44	297	62	1·51
63	1	150	1·90	6·57	283	56	1·46
65	2	990	4·50	6·30	269	46	1·42
66	2	220	2·75	6·30	309	76	1·49
67	7	360	3·00	6·44	235	59	1·13
68	1	405	3·70	5·96	274	67	1·33
69	1	380	3·50	6·16	339	70	1·72
71	1	440	4·10	6·37	305	71	1·50
72	1	433	2·10	6·16	302	76	1·45
73	1	220	4·50	5·82	347	59	1·85
74	1	400	2·20	6·16	255	56	1·28
75	1	460	3·20	6·37	297	67	1·47
76	1	330	2·80	6·16	260	62	1·27
77	1	280	3·50	5·48	305	53	1·62
79	1	720	2·80	6·91	258	53	1·31
80	1	235	2·95	5·82	304	57	1·58
81	2	91	3·40	3·91	423	63	2·31
82	1	385	4·10	6·16	308	76	1·49
83	1	170	3·80	4·25	329	48	1·80
84	1	315	2·70	6·16	288	64	1·44
87	1	470	2·90	6·44	249	55	1·24
88	1	855	2·90	7·05	239	62	1·13
89	1	560	2·80	6·51	274	59	1·38
90	1	350	2·90	6·64	294	76	1·40
91	2	426	1·85	6·52	274	66	1·33
92	1	265	2·40	6·44	300	78	1·42
93	3	490	3·00	6·71	280	67	1·37
94	1	590	3·80	6·70	287	71	1·38
95	3	590	2·40	6·51	269	61	1·33
96	8	225	5·90	5·62	316	50	1·71
97	1	470	2·50	6·51	204	28	1·13
98	1	260	2·70	5·89	276	70	1·32
99	1	555	3·00	6·44	286	77	1·34
100	1	680	3·20	6·51	274	50	1·44
103	1	450	2·40	6·71	232	53	1·15
104	2	275	3·30	5·55	263	60	1·30
105	1	480	4·00	6·54	280	66	1·37
106	1	415	3·75	6·09	363	73	1·86
107	1	310	2·60	6·51	246	62	1·18
108	1	450	2·60	6·54	274	86	1·21
109	1	225	3·00	5·89	288	80	1·33
110	1	480	2·70	6·57	298	67	1·48
111	1	350	2·80	6·37	364	90	1·76
112	1	690	3·30	6·64	242	64	1·14
113	1	800	2·20	6·37	294	70	1·44
114	1	690	2·60	6·37	295	67	1·46
116	1	190	2·70	6·67	354	100	1·63
118	1	380	3·00	6·33	342	90	1·63
119	2	298	3·00	6·78	263	70	1·24
120	1	540	4·10	—	287	52	1·51
121	1	250	4·10	5·45	286	48	1·53
122	2	930	3·40	6·37	259	76	1·17
123	1	235	2·50	5·55	315	104	1·35
124	1	430	3·50	6·02	259	65	1·24
125	1	445	1·80	5·78	270	81	1·21
126	2	620	3·70	6·88	262	76	1·19
127	5	730	3·75	6·60	287	75	1·36
128	1	375	3·25	6·67	271	63	1·33
129	1	455	3·05	6·41	293	95	1·27
130	1	630	3·80	6·19	308	77	1·48
131	1	420	2·00	6·30	269	65	1·31
132	1	450	3·20	6·44	302	73	1·47
133	1	275	2·10	5·62	371	76	1·89
134	1	390	3·60	5·96	287	70	1·39
135	2	555	3·50	5·89	290	48	1·55
136	5	270	2·40	6·60	281	76	1·31
137	2	350	2·70	6·60	283	64	1·40
139	1	510	3·60	6·37	292	60	1·49
140	1	570	3·20	6·74	255	60	1·25
141	1	420	3·40	6·85	323	75	1·59
142	3	450	2·85	6·57	301	70	1·48
143	1	270	3·50	6·02	290	68	1·42
144	1	370	3·50	6·30	301	72	1·47
145	1	670	4·00	6·30	277	55	1·42
146	3	265	4·60	6·54	321	78	1·56
147	7	880	4·35	6·54	263	70	1·24
148	1	1,034	3·50	6·00	260	63	1·26
149	1	225	2·20	6·02	318	64	1·63
150	1	260	1·60	6·19	277	70	1·33
152	1	575	2·25	6·37	267	67	1·28
153	1	545	2·30	6·78	253	68	1·19
154	1	310	2·30	6·64	299	81	1·40
155	1	550	5·00	6·64	320	91	1·47
156	1	330	3·50	6·16	335	73	1·68
157	4	560	3·00	6·44	294	70	1·44
160	1	375	1·70	6·33	309	71	1·53
163	1	518	3·65	6·44	290	58	1·49
164	8	610	3·10	6·30	300	72	1·46
165	1	400	2·90	6·57	283	72	1·35
166	1	615	4·40	6·41	346	79	1·71
167	1	690	4·10	6·41	307	58	1·60
168	1	440	2·35	6·30	293	69	1·44

TABLE II.—*(Continued)*

Case No.	No. of Pregnancy	Volume (ml.)	Fat (g./100 ml.)	Lactose (g./100 ml.)	Total N. (mg./100 ml.)	N.P.N. (mg./100 ml.)	Protein (g./100 ml.)
169	1	465	3·15	6·57	290	66	1·44
170	1	220	5·00	5·62	365	73	1·87
172	3	583	2·75	6·46	274	64	1·35
173	1	450	4·65	6·02	312	70	1·55
175	1	210	2·35	6·64	239	60	1·15
176	1	124	5·30	5·34	340	59	1·80
178	1	290	3·30	5·89	330	70	1·67
179	1	535	2·70	6·37	251	57	1·24
180	1	360	2·65	6·44	293	53	1·54
181	1	431	3·00	6·60	315	67	1·59
182	5	270	5·00	5·48	303	54	1·60
183	1	390	3·20	6·26	316	76	1·54
184	1	565	3·90	6·30	337	68	1·73
185	1	102	2·15	6·30	347	102	1·57
186	1	482	2·95	6·34	265	75	1·22
187	1	380	2·30	6·78	262	65	1·26
188	1	395	3·30	6·54	282	73	1·34
189	1	76	2·10	5·75	315	62	1·62
192	1	530	3·20	6·64	223	51	1·10
194	1	367	4·60	6·25	372	82	1·86
200	1	356	3·50	7·10	262	69	1·24
204	1	230	4·30	6·85	351	108	1·56
205	1	830	3·10	7·33	270	93	1·13
206	1	325	2·80	—	293	76	1·39
207	1	460	3·10	6·64	272	65	1·33
210	1	480	3·40	6·64	291	79	1·36
211	1	50	3·50	5·96	326	79	1·58
212	1	485	2·80	6·02	274	65	1·34
213	1	360	4·10	6·44	281	65	1·38
214	2	610	2·70	6·71	276	58	1·40
215	1	645	3·00	7·05	270	74	1·26
216	2	335	1·70	6·64	286	83	1·30
217	1	255	3·60	6·71	283	—	—
218	1	390	2·95	6·78	248	77	1·10
219	1	445	2·65	6·44	329	85	1·56
222	1	430	4·00	6·57	357	91	1·71
224	1	215	5·00	6·16	336	71	1·70
226	1	270	3·55	6·23	294	76	1·40
227	3	255	2·75	6·44	287	80	1·33
228	1	680	4·15	6·19	323	85	1·53
231	1	485	2·90	6·26	281	77	1·31
232	1	430	2·60	6·16	286	74	1·36
233	2	300	4·00	5·96	276	50	1·45
235	1	530	4·20	6·51	266	55	1·35
236	1	610	3·05	6·54	322	76	1·57
238	1	535	2·40	7·05	277	95	1·17

TABLE III.—*Samples From Later Than the Second Week of Lactation*

Case No.	No. of Pregnancy	Day	Volume (ml.)	Fat (g./100 ml.)	Lactose (g./100 ml.)	Total N. (mg./100 ml.)	N.P.N. (mg./100 ml.)	Protein (g./100 ml.)
236	1	20	510	3·10	7·01	260	53	1·33
35	9	21	954	3·60	6·87	266	67	1·28
234	1	21	419	4·55	6·98	250	87	1·04
159	1	22	299	4·25	6·19	270	67	1·30
224	1	22	540	4·40	7·12	277	90	1·20
158	2	27	541	4·30	6·89	196	43	0·98
183	1	28	534	3·75	7·30	215	62	0·98
224	1	28	500	4·90	—	246	53	1·24
162	1	32	615	3·55	6·78	189	54	0·87
225	1	34	488	3·50	6·98	209	57	0·97
35	9	37	935	3·55	7·01	205	47	1·01
198	1	38	681	3·70	6·92	197	50	0·94
138	2	40	475	3·40	6·50	222	57	1·06
119	2	41	308	3·50	7·08	181	54	0·81
235	1	42	440	4·70	6·16	192	38	0·99
151	1	47	743	4·15	6·96	212	70	0·91
199	3	47	471	3·55	6·71	224	57	1·07
116	1	48	530	2·60	7·05	216	59	1·01
161	2	48	481	2·05	6·78	172	40	0·85
163	1	48	957	4·15	7·02	209	55	0·99
115	1	49	302	1·45	6·92	196	56	0·90
74	1	50	560	2·55	7·18	185	62	0·79
102	2	50	523	3·25	7·01	191	48	0·92
139	1	50	954	3·80	6·87	195	52	0·92
110	1	53	511	2·95	7·12	183	52	0·84
177	3	53	633	3·25	6·57	235	49	1·19
205	1	58	950	4·50	6·85	197	62	0·86
121	1	62	775	4·65	6·71	189	52	0·89
174	1	62	443	3·45	6·75	192	50	0·91
75	1	135	762	4·00	7·07	144	39	0·67

breasts were emptied so that no residual milk from the previous 24 hours would be included in the sample. The methods of analysis have been detailed in Part II of this paper (see *Journal*, January 23, 1954, p. 175). Protein was estimated by multiplying the protein nitrogen by 6.41 (Escudero, 1946).

Results

The values for milk volume and for fat, lactose, total nitrogen, non-protein nitrogen, and protein contents are shown in Tables I, II, and III, arranged in order of the day of lactation they represent.

Volume.—For the first few days the yield is usually very small, but it rises rapidly from the point where, clinically, the milk "comes in." It is obvious from the small numbers of samples and from their range of values that a curve of average values would have little significance in practice, and the construction of such a curve has not been attempted. The volumes from the subjects providing the more mature samples are not likely to provide a representative picture of the volumes secreted at this stage of lactation, since some of these women were emotionally upset, either because their babies were ill or because they were experiencing some feeding difficulty. This effect has been discussed in Part I of this paper.

Nitrogen.—The findings of previous authors are broadly confirmed. There is a rapid drop in total nitrogen during the first three days of lactation, and this can be clearly seen in the Chart, where the total nitrogen contents of the milk on a number of days during the first nine days are shown for four subjects. After the third day the drop is more gradual. The mean value for 150 samples on the seventh day was 296 ± 38 mg. per 100 ml.; for 15 samples obtained between the third and sixth weeks, 225 ± 33 mg. per 100 ml.; and for 15 samples taken later than the sixth week, 196 ± 26 mg. per 100 ml. The non-protein nitrogen constitutes between 20 and 30% of the total nitrogen, the mean proportion being about 25% on the seventh day, and about 27% in the more mature milks. For protein, the mean value on the seventh day was 1.44 ± 0.22 g. per 100 ml.; between three and six weeks, 1.07 ± 0.16 g. per 100 ml.; and after the sixth week, 0.91 ± 0.12 g. per 100 ml. The range of values from the seventh day onwards is almost constant, the coefficient of variation remaining at about 15%.

Lactose.—The lactose content shows a rise during the first week of lactation, but there may be considerable fluctuations from day to day in the same subject, in contrast to the smoothly progressive trend shown by total nitrogen. Table IV shows the lactose content of milks from four subjects whose milk was examined daily during the first eight days. At seven days the mean value for 150 samples (Table II) was 6.29 ± 0.45 g. per 100 ml. and for mature milk (Table III), 6.87 ± 0.26 g. per 100 ml. There is no significant change in the mean lactose content after about the first month of lactation, and the final mature value is probably reached at about this time. The range of variation diminishes as the milk matures.

TABLE IV.—*Lactose Content of Milk in g. per 100 ml. During the First Week of Lactation in Four Subjects From Whom Serial Samples Were Obtained*

Case No.	Day of Lactation							
	1	2	3	4	5	6	7	8
172	—	5·38	5·65	6·01	6·44	6·47	6·64	6·46
224	5·21	6·26	6·37	6·34	6·51	5·96	6·16	—
233	3·97	4·11	6·37	6·47	6·02	6·16	5·96	5·96
236	—	6·57	6·09	6·19	6·23	6·44	6·54	6·82

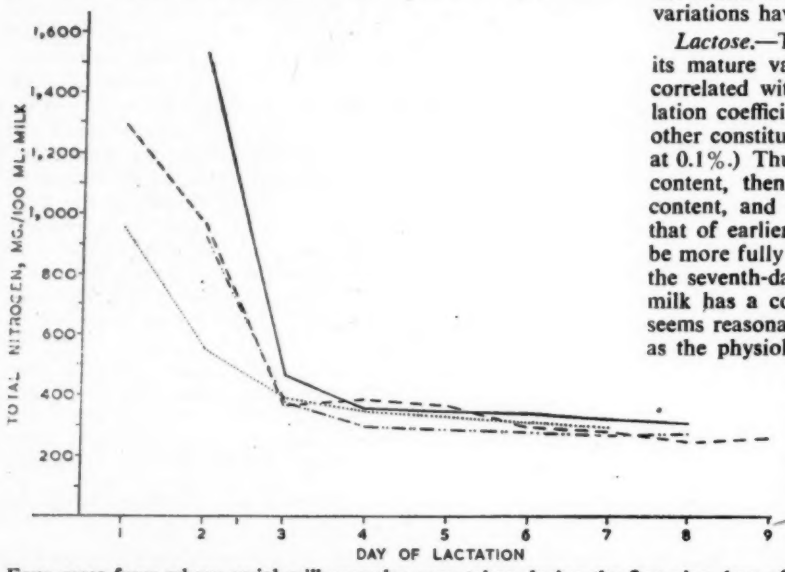
Fat.—It is not surprising that no consistent trend has been found for the fat content of milk, since the differences from one subject to another are so great that a large number would have to be examined to give a mean which would have any statistical validity. For this reason, data from the few subjects from whom samples were obtained at intervals give a clearer indication of the direction of any trend.

Table V shows the fat contents of the milk of the four women from whom serial samples were taken up to and beyond the end of the first week of lactation, those samples obtained after the second week having been expressed manually. On the first day the fat content is usually low, although one of the subjects produced 15.65 g. per 100 ml., the highest percentage of fat recorded in a 24-hour specimen. After the first day the fat content tends to rise, but there are large fluctuations from day to day up to the end of the first week, after which values become more stable. During the first week the absolute quantity of fat produced in 24 hours rises progressively, but the rate of increase is not enough to

TABLE V.—*Trend of Fat Content of Milk (g./100 ml.) in Four Subjects From Whom Serial Samples Were Obtained*

Case No.	Day of Lactation											
	1	2	3	4	5	6	7	8	9	14	21	28
172	—	1·90	3·45	2·70	3·55	2·90	2·75	3·05	—	—	—	—
224	15·65	6·35	3·85	2·80	3·50	4·60	—	—	—	4·20	4·40	4·90
233	2·65	3·55	2·90	2·80	4·40	2·40	4·00	4·20	4·00	—	—	—
236	—	0·50	1·90	2·60	2·95	2·80	3·05	2·80	—	3·10	—	—

maintain a stable fat content in the more rapidly increasing total milk yield. The trend beyond the end of the first week is illustrated by Table VI, in which 11 subjects, from whom samples were collected on the seventh day and again later in lactation, are detailed. The day of lactation on which the second specimen was taken is shown in the last column.



Four cases from whom serial milk samples were taken during the first nine days of lactation, showing the steep drop in total nitrogen content which occurs in the first three days, after which there is a gradual fall and a convergence to a narrow range of values.

It is clear, even from these few samples, that there is a rise in the fat content of milk beyond the seventh day, but, more important, Table VI shows that, unlike nitrogen and lactose, there is no tendency for the range to narrow towards what might be a physiological norm. The difference which occurs between subjects at the seventh day is maintained, and there is a high correlation between the fat contents of the seventh-day milks and the fat contents of more mature milks ($r = +0.88$). There does not appear to be a continuous rise, because mature samples taken two or three months after the seventh day show no greater increment than those taken after an interval of only a month. It is likely, therefore, that the mature fat content of the milk is reached by the beginning of the second month of lactation.

TABLE VI.—*Fat Content of Milk on the Seventh Day and in Mature Milk in Eleven Subjects*

Case No.	7th Day Fat (g./100 ml.)	Mature Milk	
		Fat (g./100 ml.)	Day of Collection
74	2·20	2·55	50
75	3·20	4·00	135
110	2·70	2·95	53
116	2·70	2·60	48
119	3·00	3·50	41
121	4·10	4·65	62
139	3·60	3·80	50
163	3·65	4·15	48
183	3·20	3·75	28
205	3·10	4·50	58
235	4·20	4·70	42

Discussion

Volume.—The few results presented here conform broadly to the accepted picture. The enormous range of milk outputs is well recognized clinically, and has been studied in far greater numbers by the indirect method of test-weighing the baby.

Nitrogen.—The decline in the content of total nitrogen which occurs during the progress of lactation has never been explained. It has been suggested that the initially very high protein content, showing as it does a preponderance of globulin, is due to equilibration with the blood of milk secreted during pregnancy and lying in the acini. But this mechanism cannot explain the further decline which occurs after the milk is being secreted in large volumes. On the seventh day the protein content varies considerably, and in some subjects it is still as high as that found typically on the fourth or fifth day. By the end of the first month these variations have practically all disappeared.

Lactose.—The rate at which the lactose content reaches its mature value also varies, and the values are inversely correlated with total nitrogen content. (The partial correlation coefficient of lactose with total nitrogen, volume and other constituents remaining constant, was −0.49, significant at 0.1%.) Thus, if milk on the seventh day has a low lactose content, then it will almost always have a high protein content, and the milk secretion as a whole will resemble that of earlier lactation. This difference in maturation will be more fully discussed in Part V of this paper, dealing with the seventh-day milk alone. The lactose content of mature milk has a coefficient of variation of less than 4%, and it seems reasonable to consider the value of 6.9 g. per 100 ml. as the physiological norm for the species.

Fat.—There can be little doubt from the figures presented that the fat content of milk increases from the beginning of lactation up to the second month. The fluctuations which occur during the initial stages of lactation appear to be due to an asynchronism between the increasing fat production and the more rapidly increasing total yield of milk, suggesting that there is a separate mechanism for the control of fat secretion. The differences in fat content on the seventh day seem to be the expression of individual characteristics and are not due, like differences in nitrogen and lactose contents, to differences in the speed of maturation of the milk. The fact that these individual differences in fat production are maintained throughout lactation means that the seventh-day sample can be used as a reliable index of the general level of fat production. For example, if the fat content of the milk on the seventh day is low, it will be low at any subsequent point in lactation.

In view of the above findings, it seems worth while to examine the meaning of the word colostrum in relation to human lactation. The colostral period has been defined in the past by a number of authors as varying from three to twenty days, and some have refined the division still further by adding, between the colostral and the mature milk, a period for "transitional milk." It is impossible to fix a time for the colostral period, such as the first seven days, since a number of subjects will be producing milk within this period which is chemically similar to mature milk. It would appear, therefore, that if a term is required which will indicate an immature secretion, then it should be based on the chemical characteristics and not on some arbitrary date-line. Since the term seems to have little practical value in clinical medicine it is not intended to suggest any criterion by which it could be redefined.

Summary

Fat, lactose, total nitrogen, and non-protein nitrogen have been estimated in 240 24-hour samples of milk collected at different stages of lactation from 194 subjects.

During the first week of lactation there is a wide range of values for total milk yield, and for all the constituents examined.

The yield rises rapidly during the first week and more slowly thereafter; the lactose content rises from an initially low level to a stable level of about 6.9 g. per 100 ml. within the first month of lactation; total nitrogen and protein content fall steeply from an initially high level during the first three days and then much more slowly until at least the second month.

The fat content is usually low during the first few days of lactation, but increases slowly to a level which is characteristic of the individual by the second month. The value, however, is stable enough by the seventh day to indicate fairly accurately the fat content of the mature milk in the individual case.

The use of the term "colostrum" is discussed.

I am grateful to Professor Dugald Baird, to the staffs of the Midwifery Department, the Aberdeen Maternity Hospital, the Royal Aberdeen Hospital for Sick Children, and to Miss G. Winship, of the Aberdeen Mother and Baby Home, for invaluable help; to Dr. I. Leitch, of the Commonwealth Bureau of Animal Nutrition, Bucksburn, for criticism and advice; and to Dr. F. H. C. Marriott for statistical assistance.

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V. INDIVIDUAL DIFFERENCES IN COMPOSITION OF MILK

When all the variations in milk composition which may be due to sampling methods have been eliminated so far as is possible by the taking of 24-hour samples under specified standard conditions (see Part III), the composition of the milk yielded by different individuals varies widely. The study of this variation has been confused in the past by the use of unreliable sampling methods or by the selection of such unrepresentative subjects as professional wet-nurses. There is still a widely held belief that the composition of human milk varies very little, and this point of view has been summed up by Bourne and Williams (1953) as follows: "Researches on the quality of milk, that is the percentages of the main constituents, show that there is not much variation, even under harsh nutritional or other conditions or when the quantity is seriously falling." In the lay mind, on the other hand, the quality of milk is often blamed for unsatisfactory breast-feeding; a plentiful milk supply with a baby losing weight seems to be a not uncommon clinical syndrome.

It has been shown in Part IV of this paper that by the seventh day the composition of milk is stable enough in the individual case to indicate the composition of the mature milk. Detailed studies of individual variations in the seventh-day milk are here discussed.

Methods

All the subjects were in the lying-in wards of the Aberdeen Maternity Hospital. It is necessary to limit studies of individual variation to milks obtained at one period of lactation in order to minimize differences of maturity. The seventh day of lactation was chosen for the reason indicated above and because there was a day or two in which to re-establish the infant at the breast after the 24-hour break, before the mother was discharged from hospital. In addition to these considerations, it is desirable to obtain milk as early as possible in lactation, because breast milk of low calorie value is likely to be replaced before long by artificial feeds, and then will not be available for analysis.

Analyses were carried out on seventh-day milk from 121 primiparae and 29 multiparae. For six of the latter, volume and fat content of the seventh-day milk were known for a previous lactation.

The methods of milk collection and chemical analysis have been detailed in Parts I and II of this paper. The calorie value was calculated by using the factors 9.0, 3.75, and 4.0 for fat, lactose, and protein respectively. (The absolute calorie equivalents for human milk are not known, but the above factors are likely to be accurate enough for present purposes.)

Results

The results of the analysis of 150 samples collected on the seventh day have already been given (Part IV, Table II). There was no statistically significant difference in average volume and composition between the 121 primiparae and 29 multiparae.

The fat content and volume of seventh-day samples of milk obtained from six subjects during their first lactation in 1949 and during a subsequent lactation in 1952 are shown in the accompanying Table. No consistent trend can be seen in the Table, but it is curious that in each subject the fat content is different in the two lactations. There is also some clinical evidence of gross differences between lactations of the same woman. Subject 161, for example, had fed her first baby for eight months with great ease (the milk was not analysed), but in the second lactation, although the milk yield was adequate, the baby lost weight and the fat content at seven weeks was found to be only 2.05 g. per 100 ml.

Fat Content and Volume of Milk During Two Lactations

Subject No.	Fat (g./100 ml.)		Volume (ml.)	
	1949	1952	1949	1952
52	2·40	1·70*	765	695*
65	3·60	4·50	880	990
66	2·50	2·75	158	220
70	3·30	2·00	910	710
122	2·75	3·40	1,100	930
227	2·50	2·75*	100	255*

* Third lactation; the remainder from 1952 are second lactations.

It is clear that more data will be needed to understand changes with parity; meanwhile analyses of individual differences will be restricted to the results from the 121 primiparae.

The mean values, together with their coefficients of variation (to illustrate the relative variability), are as follows:

		Coefficient of Variation
Volume	414 ± 172 ml.	41·5%
Fat	3·17 ± 0·78 g./100 ml.	24·6%
Lactose	6·29 ± 0·45 g./100 ml.	7·2%
Total nitrogen	296 ± 38 mg. 100 ml.	12·8%
Protein	1·44 ± 0·22 g./100 ml.	15·3%

The mean calorie value, which is very closely associated with the fat content ($r = +0.97$), was 578 ± 73 calories per litre.

The frequency distributions of values for volume and for fat, lactose, and total nitrogen contents are shown in Figs. 1, 2, 3, and 4. The curves for volume and fat are not significantly different from normal. The distribution of values for lactose is skewed to the left (there is an excess of low values) and significantly so ($P<0.05$), and the distribution of values for total nitrogen is obviously skewed to the right (an excess of high values), although the deviation from normal is not statistically significant. These deviations from a truly normal distribution suggest that there is a physiological upper limit to lactose content and a lower limit to protein content.

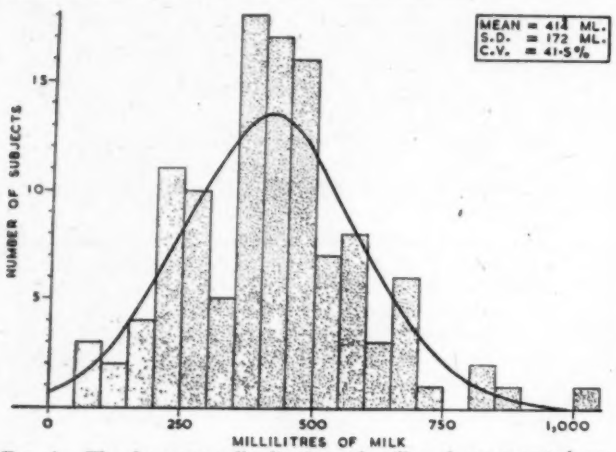

FIG. 1.—The frequency distribution of milk volume secreted on the seventh day. The normal curve is superimposed.

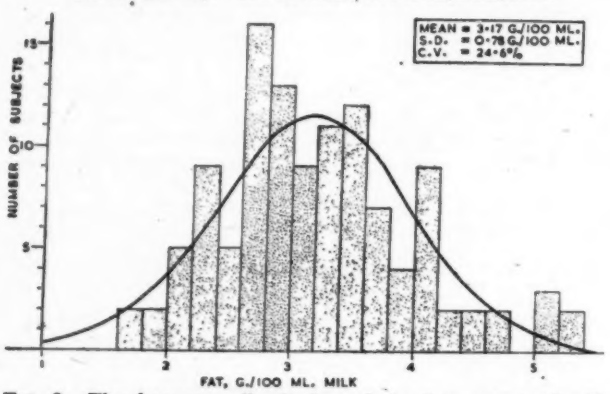

FIG. 2.—The frequency distribution of the fat content of milk secreted on the seventh day. The normal curve is superimposed.

Tests were applied to discover to what extent values for the several constituents were related to each other.* Briefly, it was found that the fat content of a given milk sample is virtually unpredictable without direct analysis. On the other hand, milk produced in large volume is likely to have a high lactose content and a low protein content, and vice versa.

Discussion

It has been pointed out in Part IV of this paper that, when samples from different individuals are considered, the values for the fat contents cover a wide range at all stages of lactation, but that the lactose and protein contents, although they may show a wide range in early milk, converge to within narrow limits as the milk matures. This is confirmed by the present study of the seventh-day milk: the fat content is clearly independent of volume and of lactose and protein, which are equally clearly closely concerned with each other. Simplified, the results indicate that if the volume of a sample is low then the lactose content is likely to be low and the protein content to be high; or that if one of these values is "immature," then the milk as a whole will be "immature." It therefore seems that the differences which are found in lactose and protein content on the seventh day of lactation are due to variation in the maturity of the milk. The skewness of the frequency distributions for the values of lactose and total nitrogen also lends support to this view, the longer tail of the graph comprising those milks which are maturing more slowly (and are therefore relatively immature at the seventh day), and the more abrupt drop at the other end indicating that a physiological norm is being approached.

Since the fat content of milk retains its wide range of values throughout lactation, it is reasonable to suppose that in mature milk there will be a distribution of fat similar to that shown in Fig. 2, shifted by perhaps 0.5 g. per 100 ml. to the right to accommodate the increase in concentration which occurs as the milk matures. On this basis there will be about 20% of women whose mature milk will have a fat content of 3 g. or less per 100 ml., and a calorie value of 570 calories or less per litre. Assuming that these women are capable of producing a litre of milk daily, which is a high yield (Morrison, 1952), and assuming that the calorie requirements of an infant are 115 calories per kg. body weight (Smith, 1951), then one-fifth of the lactating population will be incapable of adequately nourishing an infant beyond a weight of 11 lb. (5 kg.). The mother who explains her lactation failure by saying "my milk was too thin" may, in fact, be telling the truth.

The reason for these individual differences in fat content is at present obscure. That it should be a peculiarly human characteristic is understandable, since alternative methods of rearing an infant have probably always been available, either by wet-nursing or by artificial feeding, so that selective breeding for the ability to breast-feed, which has occurred in other mammals, has been avoided. However, although the level of fat production is an individual characteristic, it does not appear to be entirely genetically determined, since it is not always maintained in subsequent lactations.

In a later publication the relation of the fat content to a number of physical attributes of the mother, and also to some environmental factors, will be examined.

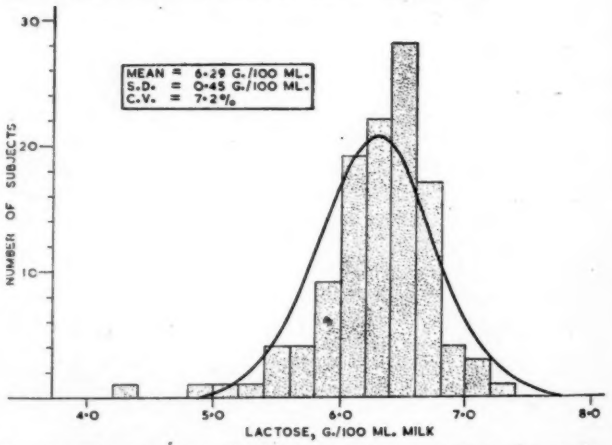

FIG. 3.—The frequency distribution of lactose content of seventh-day milk. The normal curve is superimposed.

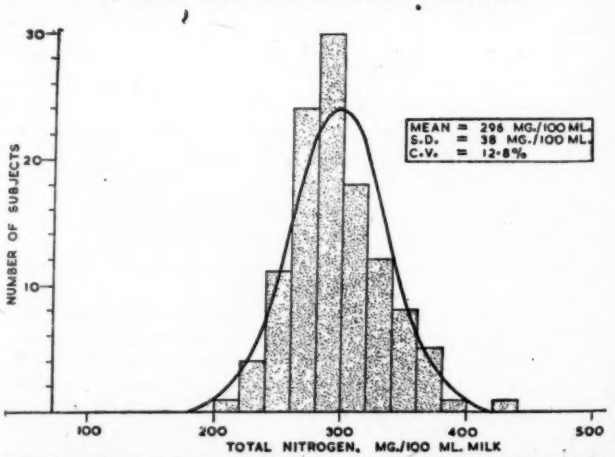

FIG. 4.—The frequency distribution of total nitrogen content in seventh-day milk. The normal curve is superimposed.

*The regression equations are:

(i) Fat = 1·90 (protein) + 0.0010 (volume)
±3.33 ±0.0004

(The effect of lactose was negligible). The standard deviation about the regression line was 0.70, compared with 0.78 for the standard deviation for fat content about its mean.

(ii) Lactose = −0.0062 (total N) + 0.00086 (volume) + 0.0014 (N.P.N.) + 6.80
±0.0011 ±0.00020 ±0.0003

The standard deviation about the regression line was 0.34, compared with 0.45 for the standard deviation for lactose content about its mean.

Summary

The differences occurring in the composition of milk on the seventh day of lactation have been studied in 150 women, 121 of whom were primiparae.

There is no statistically significant difference between the milk of primiparae and multiparae in this series, but evidence is presented to show that the same individual, in two lactations, may produce milk differing greatly in fat content.

There is a wide range of values for all the major constituents as well as for the total yield at this stage of lactation. The variability of the lactose and protein seems to be due to differences in speed of maturation of the milk.

There is a wide range of fat content, and consequently of calorie value. The fat content is not apparently related to the content of other constituents, and seems to be an individual characteristic. In some milks the fat content is so low that, even with a high milk volume, the child may be undernourished.

I am grateful to Professor Dugald Baird and to the staffs of the Midwifery Department and the Aberdeen Maternity Hospital for invaluable help; to Dr. I. Leitch, of the Commonwealth Bureau of Animal Nutrition, Bucksburn, for criticism and advice; and to Dr. F. H. C. Marriott for statistical assistance.

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IODODERMA OF THE FACE AND MARKED EOSINOPHILIA

BY

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Iodine has a long-established place in the history of medicine. There are few drugs which have been used more freely in the treatment of coughs, syphilis, and thyrotoxicosis, apart from its popularity as a skin disinfectant. Relatively few cases of iodism have been reported despite the commonness of its use and importance in radiological contrast substances.

The present case draws attention once again to the dangers of iodine intoxication and demonstrates two features of some interest—an unusual skin lesion and a pronounced eosinophilia.

Case Report

A 60-year-old white man of French extraction, resident in British Columbia for over 30 years, was admitted to the Vancouver General Hospital on February 27, 1952. Asthma had troubled him at infrequent intervals for many years without producing any severe disability. During 1951 he had two major surgical procedures—a suture of a perforated gastric ulcer in April and a transurethral prostatectomy in November—and during this period his general health deteriorated and his asthma became increasingly severe.

In October, prior to his prostatectomy, he was submitted to intravenous pyelography, and developed a severe but temporary reaction to the iodine-containing contrast substance. In November, for a four-week period following his operation, he was given 5 gr. (0.32 g.) of potassium iodide three times a day in an attempt to avoid any fibrous contraction of the prostatic bed. During January, 1952, his asthma became more troublesome. Towards the end of the month he treated himself with proprietary asthma tablets, each containing about 1½ gr. (0.1 g.) of potassium iodide. He took an average of six tablets daily. A few days after beginning this treatment he noticed red vesicular raised spots appearing on his arms and trunk. He described them as being like "pimples from which no pus came." By the middle of February he had developed several spots on each malar region, and these gradually spread and coalesced to form fungating tumour-like masses. These lesions and his severe asthma caused his admission to hospital.

Physical examination on admission showed a firm raised reddish mass with an irregular surface over each malar region of the face; severe asthma with an emphysematous chest; hypertension (B.P. 190/108); and a few vesicular spots on the upper trunk and arms.

Laboratory studies on February 28 showed: Hb, 97%; W.B.C., 32,950 (P. 22%, staffs 1%, lymphs 6%, monos 4%, eosins 66%, basophils 1%); N.P.N., 38 mg. per 100 ml. Urinalysis: Sp. gr. 1022; protein +++; W.B.C. ++; R.B.C. ++; and an occasional hyaline cast seen.

During the week February 28 to March 6 the patient's condition steadily deteriorated and oxygen was given continuously. Treatment included adrenaline, aminophylline, penicillin, and potassium iodide—5 gr. (0.32 g.) three times a day. Bacteriological examination of the facial lesions on three occasions revealed the presence of only coagulase-negative *Staphylococcus albus*.

A sternal puncture and haemogram were performed on March 4, the findings being:—(1) Peripheral blood: Hb, 98% (14.2 g.); R.B.C., 5,300,000; platelets, 350,000; reticulocytes, 1%; haematocrit, 44%; W.B.C., 31,800 (neut. polys 16%, neut. staffs 2%, eos. polys 55%, eos. staffs 15%, lymphs 8%, monos 4%). (2) Bone marrow: On a 300-cell differential count 37.3% were lobed eosinophils, 11.3% staff eosinophils, 4.3% metamyelocyte eosinophils, 5% myelocyte eosinophils, and 0.6% promyelocyte eosinophils. The marrow was not as hypercellular as one would expect in a leukaemic condition, and in view of this, the absence of splenomegaly, and the excessive rarity of eosinophilic leukaemia it was felt that the latter was probably not the diagnosis.

On March 6 the patient was seen with a view to the possible administration of A.C.T.H. as a life-saving measure. His condition was critical. The striking lesions on the face had extended and the surface was now a blackish-red colour (Fig. 1). He was in an oxygen tent, his breathing was asthmatic and very laboured and noisy, and he was roused only with difficulty, his answers to questions being irrational. In addition to hypertension he had a marked tachycardia (pulse rate 160) with numerous extrasystoles. Examination of the upper trunk and arms revealed the presence of numerous rounded raised red papular spots of varying size, while similar spots were evident on the chin and ears.

FIG. 1.—Photograph of patient showing facial lesions.

The patient was put at once on intravenous A.C.T.H., digitoxin, pethidine hydrochloride, and diphenhydramine hydrochloride, the pre-

vious drug treatment being stopped. After 48 hours under this regime he showed marked improvement, oxygen was discontinued, and a steady uneventful recovery was made.

The day following the change in treatment the full story of iodine intake was obtained and the diagnosis made of iododerma, the facial lesions being typical of some previously described in this condition.

A biopsy from one of the facial lesions was taken. The pathologist reported: "The surface of the lesions is covered by hyperkeratosis and parakeratosis. Extending deeply into the underlying cutis there is marked epitheliomatous hyperplasia with both large and small epithelial pearls. In the centre of many of the smaller projections are minute micro-abscesses. Despite this irregular and marked acanthosis, however, the constituent cells are well differentiated and prickle-cell bridges can be demonstrated. Nowhere does the lesion suggest cytologically a squamous-cell carcinoma, though the picture superficially is somewhat similar. The dermis in both the superficial and deeper parts of the lesion suggests a fibrosis and is heavily infiltrated with subacute and chronic inflammatory cells. The picture is consistent with a diagnosis of iodism."

In all only 85 mg. of A.C.T.H. was given intravenously over a period of eight days, the infusion being kept going almost continuously. The effect of the A.C.T.H. on the eosinophils and 17-ketosteroids is illustrated in Fig. 2.

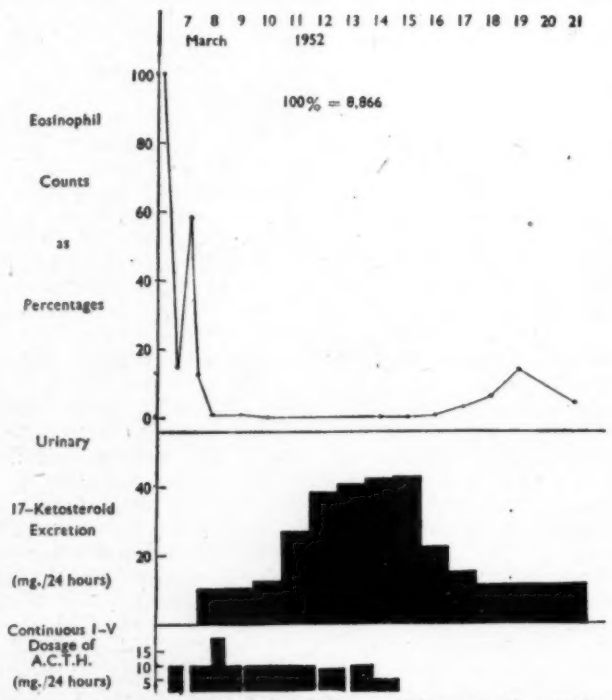

FIG. 2.—Showing effect of A.C.T.H. on 17-ketosteroid excretion and eosinophils.

During the recovery period the facial lesions slowly regressed. The asthma improved greatly without being completely relieved, while the pulse rate fell to between 80 and 90. The albuminuria remained +++ for about a week, and then gradually subsided, only a trace of albumin being noted on March 20, the day before discharge.

The patient was readmitted three weeks later for further study. At that time his total eosinophil count was about 1,000 per c.mm., his asthma was still troublesome, but the facial lesions had completely disappeared apart from some slight residual pigmentation of the skin. There was no albuminuria.

Comment

This case presents several unusual features which stimulate speculation on the mechanisms involved. Reactions to drugs can be broadly divided into two types; (1) toxic signs and symptoms due to acute or chonic overdosage; and (2) signs and symptoms due to a personal idiosyncrasy producing hypersensitivity to the drug. In this particular case there are features of both types of reaction. The vesiculo-papular rash and tumour-like masses are recognized features of iodism due to chronic intoxication with the substance, while the sharp reaction to the pyelography and the very high eosinophilia of the later acute illness both suggest a hypersensitivity type of reaction. It is interesting to note that two months after the reaction to the pyelography a four-weeks course of potassium iodide produced no obvious symptoms, but after the beginning of the second course, six weeks later, the rash appeared almost immediately. The first course appeared to be a "sensitizer" which resulted in a hypersensitive response to the second. Seymour (1937) reported a similar effect with iodine applied to the skin. A 7.5% tincture was used for the skin preparation for the induction of an artificial pneumothorax. After the sixth treatment a rash developed which settled in a few hours. Eleven days later the procedure was repeated, and within a week the patient was dead from an exfoliative dermatitis.

The marked eosinophilia in the present case supports the idea of a sensitivity reaction. The patient was susceptible to allergic manifestations, being a chronic sufferer from asthma. As such he may have had a moderate eosinophilia for years, but the level of the eosinophils in the blood in this acute illness was much higher than normally found in asthma *per se*. Iodine in the blood stream is largely bound to protein. "Foreign protein" is regarded as exerting a "chemotactic stimulus" to the production of eosinophilia (Whitby and Britton, 1947). One may postulate, therefore, that in this hypersensitive individual the iodine-protein complex has acted as a "foreign protein."

During the past 20 years two clinical entities have been described in which asthma and extreme eosinophilia are the main features. These are Löffler's (1936) syndrome and tropical eosinophilia. Apley and Grant (1945) thought there was a good case for classifying them under the one heading "eosinophilia with pulmonary disease" or the "E.P. syndrome." Two cases of this syndrome have been reported due to chronic brucellosis (Elsom and Ingelfinger, 1942). Herbert *et al.* (1950) have observed a difference between the two conditions in their response to A.C.T.H. therapy. The present case also shows the main features of the syndrome, and a clear aetiology. It supports the suggestion that the "E.P. syndrome" is probably a non-specific response to a variety of different hypersensitive conditions.

It is difficult to assess the role of A.C.T.H. in this patient's recovery. It seems possible, however, that the hormone did accelerate it. It is of interest to observe the satisfactory response to relatively small amounts of A.C.T.H. administered by slow and almost continuous intravenous infusion. In a previous paper (Cape *et al.*, 1952) it was shown that the minimum intravenous dose of A.C.T.H. given in this way which produced a maximum effect on the eosinophils was about 0.2 mg. per hour. Approximately double this dose was given in the above case with entirely satisfactory results. The fact that this dose will not produce a maximum stimulation of adrenal steroid production suggests that adequate therapeutic responses may be obtained without such full stimulation. The effect on the peripheral eosinophils was dramatic, as in less than 48 hours the count had fallen to 19 per c.mm. from almost 9,000. (See Fig. 2.)

After stopping A.C.T.H. the eosinophils rose to a level varying between 600 and 1,000. This level appeared to be fairly stable, as on the second admission three weeks later it was 1,000. This is consistent with the eosinophilia seen in chronic asthmatics and suggests that this patient did normally have an increased level of the cells in his blood.

The significance of the urinary findings in the acute stage of the condition was not entirely clear in view of the previous history of prostatic trouble. However, older records showed that, while some white cells and a trace of

protein were present in the urine following the prostatectomy, no red cells were found. This and the manner in which the urinary abnormalities cleared up during the recovery period indicate that the iodism was accompanied by a moderately severe degree of an acute renal disturbance, part of a generalized allergic reaction.

Summary

A case of iododerma, with striking facial lesions, is described. The patient was a severe asthmatic treated, *inter alia*, with potassium iodide. Hypersensibility to the iodine resulted in skin lesions, a marked eosinophilia, tachycardia, and proteinuria.

Recovery followed the withdrawal of iodine and the administration of A.C.T.H.

The mechanism of the intoxication is discussed with particular reference to the significance of the eosinophilia. A comment is made on the so-called "E.P. syndrome" and on the effect of A.C.T.H. in the recovery of the patient.

I would like to thank Dr. A. S. Turner for permission to publish this case, and Dr. R. A. Palmer, director of the metabolic unit, Vancouver General Hospital, for his stimulating advice and criticism.

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PRE-ERYTHROCYTIC STAGES OF HUMAN MALARIA: PLASMODIUM OVALE

A PRELIMINARY NOTE

BY

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Four species of malaria parasites are found in man—*Plasmodium vivax*, *P. falciparum*, *P. malariae*, and *P. ovale*. Pre-erythrocytic stages of *P. vivax* were demonstrated by Shortt *et al.* (1948) and of *P. falciparum* by Shortt *et al.* (1949) and Jeffery *et al.* (1952). Elucidation of this cycle in the remaining types presents two special difficulties: (1) the comparative rarity of the parasite, and (2) the poor infections usually obtainable in mosquitoes (an essential factor for success of an experiment of this kind is a large supply of heavily infected mosquitoes). Fortunately, *P. malariae*—the agent responsible for quartan malaria—has a replica in monkeys, *P. inui*, which in length of blood cycle (72 hours), length of infection in mosquitoes, and morphology closely resembles the human form; and the demonstration by Garnham (1951) of the tissue cycle of *P. inui* probably indicates the nature of the pre-erythrocytic stage of *P. malariae*. No such simian counterpart exists in the case of *P. ovale*, and a human experiment was necessary if the problem were to be solved. A further practical difficulty to-day is the scarcity of cases of general paralysis in need of malaria therapy; practically none were available for this experiment, and, except for a short break when the infection was kept at Horton Mental Hospital, the strain had to be maintained amongst ourselves. The strain was obtained from Dr. A. R. D. Adams, who had originally isolated it from a patient from Liberia and had passed it through two patients by blood-transfer before sending it to us.

The Experiment

Repeated attempts to infect mosquitoes (*Anopheles maculipennis atroparvus*) were made, but results were poor until the last trial (on J. W.), when 84% of a batch of approximately 750 became infective, with concentrations of sporozoites in the salivary glands varying from heavy to very light. These mosquitoes were allowed to feed on one of us (W. C.) on December 18, 19, and 22, 1953; many were made to bite more than once on each day by the process of interrupted feeding. Nine days after the first feed Mr. H. R. I. Wolfe excised a wedge-shaped piece of liver (about 1½ inches at the base) from the patient's left lobe.

Sections were prepared, and revealed the presence of pre-erythrocytic schizonts of *P. ovale*. A few hours after the operation the blood of the patient became flooded with ring forms of the parasite. The tissue forms were in two stages, nearly mature and completely mature schizonts. Their morphology more resembles that of the quartan parasite than of *P. vivax*, but further study of material is necessary before a definite conclusion about the affinities of this parasite can be reached.

Acknowledgments.—We are indebted to Dr. A. R. D. Adams for providing the strain and to Sir Gordon Covell and Mr. P. G. Shute for help in maintaining it. We are very particularly appreciative of the generous help of workers in Dr. Martin D. Young's laboratory in Georgia, U.S.A.—and particularly Dr. G. M. Jeffery—for taking the strain and passing it through numerous patients and mosquitoes, for the purpose of supplying us with an infective batch of mosquitoes if our own experiments had failed. We gladly acknowledge also the invaluable assistance rendered by the surgeon, Mr. H. R. I. Wolfe, Mr. R. Molloy, anaesthetist, and Professor A. W. Woodruff, Dr. S. Bell, and other members of the staff of the Hospital for Tropical Diseases, where we were looked after with kindness and efficiency.

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—— Garnham, P. C. C., Covell, G., and Shute, P. G. (1948). Ibid., 1, 547.

The Invalid Children's Aid Association's John Horniman Home at Worthing, Sussex, will admit from next April children (girls 7–16, boys 7–14) who need holidays, or care in family crises, but are so severely handicapped that they cannot be received in ordinary convalescent homes. It is hoped to provide for such cases as those with spina bifida, poliomyelitis, congenital deformities, haemophilia, muscular dystrophy, cerebral palsy (I.Q. not below 65), fragilitas ossium, and heart disease (congenital or rheumatic if quiescent). Children suffering from mental defect, epilepsy, blindness, or pulmonary tuberculosis cannot be received. The daily programme will be designed to provide the children with as many interests as possible, and will include handicrafts, painting, modelling, and probably a Guide company and Scout troop. Physiotherapy will be available. Holidays may be arranged ordinarily up to eight weeks. Accommodation will also be available for one or two nights for mothers whose presence may help a child to settle happily. Inquiries should be directed to the general secretary of the association, Miss Rattenbury, 4, Palace Gate, London, W.8.

Medical Memoranda

Thiopentone Injection into an Aberrant Artery

The following case is reported because of its unusual character and as a warning to anaesthetists to be ever alert against the possibility of inadvertent intra-arterial injection.

CASE REPORT

The patient, a woman aged 35, was admitted for dilatation and curettage. A venipuncture was made into what appeared to be a vein in the middle of the proximal part of the ventral aspect of the right forearm (at the point marked X in Fig. 1). About 2 ml. of 5% sodium thiopentone had been injected when the patient complained of burning pain passing down the arm to the hand. Injection was stopped and the "vein" palpated; it was found that, proximal and distal to the point of injection, along the line of the "vein," pulsation could be felt. The needle was kept *in situ* and 5 ml. of 2% procaine slowly injected through it. On removal of the needle after injecting the procaine, blood issued from the puncture in little intermittent spurts. The pulse in the punctured artery was observed for some minutes; it remained unaltered. Anaesthesia was restarted and the operation carried out uneventfully. The patient was kept under careful observation for a few days before discharge; the colour, temperature, and pulses in the right arm remained unaltered.

FIG. 1.—Photograph of the patient's forearm. The black line shows the course of the aberrant vessel.

An angiogram was taken two days later (Fig. 2). It showed the aberrant vessel arising at the bifurcation of the brachial artery and pursuing its course through the forearm to the ulnar border of the wrist. It will also be seen that the brachial artery bifurcates above the level of the elbow joint.

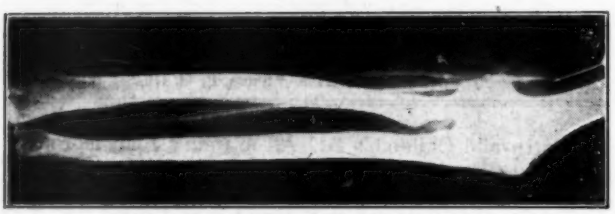

FIG. 2.—Angiogram of right forearm

COMMENT

The vessel injected in this case was almost certainly an aberrant ulnar artery. Gray (1935a) states that when the ulnar artery arises above the elbow "it is usually superficial to the flexor muscles in the forearm, lying commonly beneath the fascia, more rarely between the fascia and the skin." In the present case the vessel was certainly subcutaneous. Macintosh and Heyworth (1943) report two cases of intra-arterial injection of thiopentone, in one of which the injection was made into an aberrant ulnar artery. They also quote a further case in which thiopentone was injected into an aberrant ulnar artery (Van der Post, 1942).

Other arteries in the arm may occasionally be mistaken for veins. Thus, according to Gray (1935b), the radial artery occasionally takes a superficial course through the forearm. Again, Hewer (1944) states that sometimes "the brachial artery takes an abnormally superficial course through the antecubital fossa."

It is recommended that, in order to avoid puncturing a superficially placed artery in mistake for a vein, the vessel to be injected should always be palpated *before* the tourniquet is applied to the limb.

I am grateful to the staff of Hope Hospital, Salford, for their co-operation.

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Presternal Oedema in Mumps

The occurrence of swelling over the manubrium sterni in cases of mumps does not appear to be well known in this country, and references to it in the literature are scanty. Radin (1918) writes: "There are a few cases in which mumps expresses itself by a general swelling of neck and chest, like Hodgkin's disease, a doughy gelatinous mass. . . . There is no tenderness. The tissues are soft and elastic and are easily agitated. . . . Rarer symptoms . . . were . . . dysphonia." He presents evidence of thymus enlargement in one case with presternal oedema. Barker (1943) reported three such cases from an outbreak involving 438 persons. Two of these three had dysphagia, and in one the epiglottis and the right wall of the hypopharynx were seen to be swollen. Rappaport (1943) described two cases, both boys and both with mumps of normal severity. In an outbreak of mumps involving 502 patients at Fort Benning, Georgia (Gellis and Peters, 1944), 30 cases developed presternal oedema, two of them with dysphagia also. Twenty-five had one or both submaxillary glands swollen at the time the presternal swelling became evident, whereas the other five had parotid mumps only.

Among 263 cases of mumps encountered in a semi-rural area of Gloucestershire presternal oedema was seen five times, twice in males aged 4 and 8, and three times in females aged 4, 7, and 41. The circumstances of the study make it likely that the true incidence is far higher than these figures suggest, and that presternal oedema is as common a feature as swelling of the gonads. In our cases the oedematous area varied in size, sometimes attaining 3 in. (7.5 cm.) in diameter. The skin covering it was of a normal colour, and in at least one case pitting definitely occurred. Gellis and Peters reported that the skin became a dull red over the swelling in 3 of the 30 cases. The degree of presternal swelling was unrelated to the severity of the glandular involvement.

In describing his first case Barker mentioned that the oedema seemed to be more gelatinous than ordinary oedema and did not pit well on pressure. Gellis and Peters state that in all their cases the oedematous tissues pitted easily, and they demonstrated the fact by lateral soft-tissue *x*-ray films. Probably the swelling is due to obstruction of the lymphatic drainage, but it is a little difficult to see how this is brought about mechanically in those cases in which the parotids only are involved.

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Reviews

THE KINSEY REPORT

Sexual Behavior in the Human Female. By Alfred C. Kinsey, Wardell B. Pomeroy, Clyde E. Martin, and Paul H. Gebhard. (Pp. 842; 115 figures. 50s.) Philadelphia and London: W. B. Saunders Company. 1953.

The advertisement columns of the *Journal* have described this as "the most discussed and controversial book of the year." It has already received important notice by the more responsible press in this country, as well as lurid comment by those papers which enjoy a reputation for the unwholesome exploitation of sex and crime. It has not escaped the attentions of music-hall comedians—even those employed by the B.B.C. Indeed, the name of Kinsey is as well known to adolescent boys (and possibly girls as well) as was that of Freud in the days when their parents and grandparents were young.

This kind of introduction prejudices the reader's approach to the book; and a detached appraisal is made even more difficult because sex is so strong and basic an instinct that it cannot be viewed without an emotional bias governed by personal experience and upbringing, and, in the case of the doctor, by the disclosures of his patients. This is well illustrated by the report itself. It sets out to be an impersonal scientific statement of facts, but the authors cannot resist commenting on moral implications. They suggest, for example, that if premarital coitus were not taboo then homosexual practices might be prevented in large measure. The fact that 2,094 of their unmarried women who admitted coitus had produced 476 pregnancies is dismissed by pointing out that this means only one pregnancy in 1,000 sexual acts, and that methods of contraception are improving and becoming more widely known. Forty-four cases of venereal disease amongst these women is counted of little consequence because the treatment of these conditions is becoming more efficient. Again, figures in the report show that those men and women who have sinned according to the moral or legal codes of the community are less likely to condemn similar transgressions by others and are more likely to transgress again. Those who are sexually promiscuous before marriage are more likely to be unfaithful after marriage.

Nevertheless it should be emphasized that the approach is basically scientific and the authors have set out to supply facts to replace impressions. The report is a companion to one on *Sexual Behaviour in the Human Male*, which was also written by Dr. Kinsey and his associates of the Institute of Sex Research at Indiana University and published in 1948, and the authors have wisely included summaries of their previous findings for purposes of comparison. The book is divided into three main sections. The first provides a general historical background and describes the methods of sampling and statistical analysis used in the inquiry. The last is concerned with the anatomy, physiology, and psychology of sex and sexual responses in both male and female. Nervous and hormonal controls are discussed, and there are interesting observations on the effect of castration on sex drive. The detail given and the variety of the approaches can be judged by the fact that there are even reproductions of electroencephalographs taken during orgasm in the human being.

The middle section and the main body of the report consist of an analysis of confidential information given by 5,940 white women interviewed during 15 years up to January 1, 1950. During the same period 934 coloured women and 915 white women serving prison sentences were also questioned, but the findings among these selected groups were used only for the general information of the authors. If the 8,603 males questioned at the same time are included, the authors' views and findings can be taken generally to be based on a study of 16,392 human beings. To this may be added several other sources of information, including a large literature on both animals and man (the list of references occupies 50 pages), not to mention complete records of all the wall inscriptions found in 353 men's and women's public lavatories.

The work involved must have been considerable, for each individual was asked about 300 questions, and the duration of interview averaged 1½ to 2 hours. The writers evidently took great trouble to establish the validity of their data, but they nevertheless recognize that it is not always easy to get the truth, even from volunteers who are guaranteed secrecy by a special code system of recording. It was found in fact that there were not too many discrepancies when men's and women's statements were compared, and, interestingly enough, that women are not more likely than men to distort the truth.

The aspects of sex which are covered are both numerous and diverse. They include homosexual as well as heterosexual experiences of all types and degrees in infancy and adolescence, before and after marriage, and after the menopause. Masturbation, "petting," sex dreams, premarital coitus, extramarital coitus, marital coitus, and animal contacts, all find a place. Incidence, frequency, and techniques are considered as a whole and in relation to age, parental occupation, decade of birth, environment, and religion. No one could complain of lack of detail, and the revelations may surprise many who did not know of or did not wish to admit the existence of certain sexual practices or their extent. Much of it is disturbing as judged by accepted standards unless the reader realizes that terminology can turn an innocent kiss or a harmless flirtation into something rather sinister. Moreover, the figures do not distinguish between lust and love, and the latter is in danger of being completely overlooked.

The ultimate assessment of the reliability of the facts presented and the extent to which they can be applied can be made only by statisticians qualified to judge the methods of sampling and analysis. The authors do not claim that their findings necessarily apply to any except certain communities in their own country. To obtain their material they haphazardly approached a variety of groups of people —the staff and employees of a factory, the members of a church, college and school classes and their staffs, the members of women's organizations, patients attending a certain clinic, etc. These were distributed throughout the States and covered all levels of society in both rural and urban districts. An attempt was made to persuade all in a chosen community to give evidence, but on an average only 75% of women agreed to participate in this soul-searching and passion-probing investigation. It is natural to wonder what motives prompted some to refuse and others to comply. They might be such as to cause considerable distortion of the record in either direction. Again, the distribution of the women investigated by age and by religion is clearly different from that which obtains among the population as a whole. These and other points raise serious doubts about the selection of material.

If the statistics are accepted as reliable for the communities investigated, what is their value? People whose work brings them in close contact with human nature are already aware that the sex impulse is strong, that not all men and women are virginal at the time of marriage or faithful afterwards, and that masturbation occurs almost universally among both sexes at some stage of development. Is it any advantage to have figures which show that 62% of all women masturbate at some time in life, and which indicate the technique and incidence according to age, occupation, religion, and marital status? What value is it to learn, without full knowledge of all the attendant circumstances, that nearly 50% of married women have had premarital coitus (half of them only with their fiancé), and that 90% of women have had petting or flirting experience of one sort or another? The authors argue that "There is an honesty in science which refuses to accept the idea that there are aspects of the material universe that are better not investigated, or better not known, or the knowledge of which should not be made available to the common man." They point out, moreover, that to criticize their presentation on

the ground that it may be misinterpreted or misused is as idle as to condemn atomic scientists for the reason that their discoveries have been turned into atomic bombs. Splitting the atom, however, is a precise impersonal exercise, the validity of which cannot be put in doubt. Is this true of the mathematical dissection of sex? Cold figures take little account of the all-important context and they can distort perspective.

Knowledge for the sake of knowledge is all very well, but the dissemination of a little knowledge and the advertisement of evil can create or aggravate a problem. Would there be any "teenage" problem in the U.S.A. if parents and social workers ceased to talk of it? Would there be so many cosh boys and adolescent delinquents in Britain if crime were not reported in newspapers and gangsterism flaunted in the cinema? Might not many girls whose moral fibre is only as strong as public opinion be influenced in their behaviour by accepting Dr. Kinsey's statements on how many of their sex defy accepted codes either before or after marriage? Morality, after all, is not absolute but relative to the behaviour, opinion, and, indeed, faith of any particular community at any given epoch. And the standards of one community may not suit those of another.

Whatever view is taken of this latest import from the U.S.A.—and, as pointed out above, views will inevitably differ widely and strongly—it would be a mistake to underestimate its importance. It is not only monumental; it carries the backing of a university and has been financially sponsored by a research committee whose members include men of the highest integrity and scientific renown. This report will inevitably serve as a reference book for all concerned with human relations, and will be quoted throughout the world for many years to come. Those who use it and quote from it have a duty to do so wisely.

T. N. A. JEFFCOATE.

PHONOCARDIOGRAPHY

Fonocardiografia Clinica. By A. Caniggia. (Pp. 290; 232 figures. 3,000 lire.) Turin: Edizioni Minerva. 1953.

This book is described as a practical manual for doctors and students. In Britain clinical phonocardiography has no very general use, and in Italy this is the first monograph to be published on the subject. One may at the outset compliment the author on the clarity and elegance of the illustrative tracings; they are indeed excellent. It will be noted that the large majority of the tracings reproduced in this volume are recorded by the logarithmic method. This procedure eliminates any vibrations of too weak periodicity and increases others in a measure which is directly proportional to the sensibility of the human ear. The linear or stethoscopic technique has been used when it was thought important to stress the value of this method or to bring forward evidence of some vibrations of low periodicity. The actual tracings seem to have been done mostly by an oscillographic system which registers the differences of potential by an optical method on a photographic film; perhaps in some cases pens have been used, but it is not clear which they are. The timing is done by means of the electrocardiogram; this is chosen because of the convenience with which such a record can be obtained. Owing to technical difficulties, the jugular and carotid pressure tracings are thought to be less reliable. The author gives various examples of artifacts. He fully discusses the different sounds of the heart, and their modifications are beautifully illustrated. The effect of arrhythmias on the sounds is made very clear. There is an interesting account of gallop rhythm. As usual, in this thorny matter nomenclature introduces certain difficulties. The rest of the book is devoted to the murmurs, and very well illustrated they are. The value of this book does not rest solely on the illustrations; the text is also good. In fact we might say it is really a treatise on auscultation illustrated by phonocardiograms. The book can certainly be recommended, and the illustrations are suitable for teaching students.

TERENCE EAST.

RENAL DISEASE

Mechanisms of Urologic Disease. By Professor David M. Davis, M.D. (Pp. 156. £1 2s. 6d.) Philadelphia and London: W. B. Saunders Company. 1953.

The title of this book suggested an authoritative work on a section of the physiology of the urinary tract which has received less attention than it deserves—the mechanics and hydrostatics of the organs of the urinary system. But the author has preferred to use it to denote the way in which the whole urinary tract is affected when one of the common pathological changes involves one or more of the organs of this system. Thus the first chapter is on obstruction as it affects various organs. This is followed by chapters in a similar manner on infection, stone formation, neoplasms, congenital abnormalities, trauma, and neurogenic changes. In treating his subject on these lines the author briefly describes nearly all the commoner urological diseases and discusses the most recent treatments. But the brief way in which even the most important diseases are dismissed makes it difficult to understand for whom the book was written. The author claims that it was written for beginners and physicians who are not urological specialists, but it is unlikely to help the student pass his examinations, while the physician is unlikely to learn much he does not already know. Nevertheless its brevity allows it to be read rapidly, and the treatments described are the latest and most widely accepted. The chapter on history taking and physical examination is excellent, as is that on the technique of catheterization. This book may appeal to readers who want to refresh rapidly their knowledge of urology from a somewhat novel approach.

J. E. SEMPLE.

CHILD PSYCHOTHERAPY

Practical Child Psychotherapy: A Guide for the General Practitioner. By Curt Boenheim, M.D. Second edition. (Pp. 184. 15s.) London and New York: Staples Press. 1953.

Psychotherapy is given an unusually wide connotation in this book, which is written as a guide to the general practitioner. Children provide the most plastic material the doctor encounters, and so all re-educative methods, such as dieting, exercises, environmental changes, and parental instruction, must find a place in child psychotherapy. An exclusively psychological approach, without needed somatic treatment, is bound to fail. Dr. Boenheim holds that the general practitioner should, and indeed must, himself treat the majority of the children who require psychotherapy. Hence the aim of the book is to show the significant part played by emotion in common complaints such as loss of appetite, vomiting, enuresis, stammering, and cardiac neurosis—to mention a few of the topics discussed. Treatment by a specialist or reference to a child guidance clinic will be desirable from time to time. It is not clear where the "minor psychotherapy" conducted by the family doctor ends and that of the specialist begins.

The classification adopted is based on symptoms, and this admittedly is unsystematic. But, it is argued, when symptoms are related to the personality of the child and to environmental influences the method is practical and can give considerable enlightenment on the problem of the sick, peevish, and difficult child. Whereas relief of the symptom can often be considered successful treatment, Boenheim insists that child psychotherapy—presumably by the specialist—should be based on a clear differential diagnosis and distinct indications. There is, on the whole, too much discussion of conflicting opinions on the psychotherapy of infants and children. The family doctor will be puzzled by these, and he cannot be expected to assess their relative merits. The sections on alimentary disorders, enuresis, and stammering deserve special attention.

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ERYTIIROMYCIN

Erythromycin ("ilotycin," Lilly; "erythrocin," Abbott), which has hitherto been available in this country only in very limited quantities to hospitals in the National Health Service, will next week be freely obtainable on prescription. A statement issued by the Ministry of Health is published elsewhere in this issue (p. 270). It is more than usually important for the profession to decide what use it should make of this antibiotic. What the consequences of this decision will be depends on one entirely unknown factor, the extent of the natural resources which have yet to be tapped for further antibiotic drugs. If erythromycin is but one of a series of discoveries which is to continue—not indefinitely, for that is inconceivable, but at least for a comfortable period of years—then one can afford to use it freely, confident that when it begins to fail another will take its place. If, on the other hand, it proved that this series had come to an end, we should be well advised to husband our existing resources and to see that erythromycin retained its present inestimable value as long as possible by selective and careful use. It has already been shown[1] that its extensive use rapidly breeds a bacterial population resistant to its action.

Erythromycin has a similar "spectrum" to that of penicillin, Gram-positive organisms predominating among those sensitive to it, although these also include gonococci and other neisserias, *Haemophilus* spp. and rickettsias. There is no doubt of its efficacy in acute infections due to haemolytic streptococci or to pneumococci; thus the average acute sore throat or pneumonia will respond well to it. On the other hand, these species are also invariably sensitive to penicillin and to the broad spectrum antibiotics. It is particularly active, much more so than penicillin, against *C. diphtheriae*, and should certainly be given an extended trial in diphtheria and even in the less promising task of eliminating the diphtheria carrier state. Without question its greatest usefulness is in the treatment of staphylococcal infections resistant to other antibiotics. That these are now often resistant to penicillin is well known, and we are beginning to be familiar in this country with their resistance also to aureomycin and terramycin, although this condition is so far much less frequent than in the United States, where 36% of strains were recently found to be resistant to these antibiotics at the Mayo Clinic[2] and 61% in Seattle.[3] Such findings refer to hospitals where cross-infection is largely responsible for increasing resistance, but it is in hospital that serious staphylococcal infections often arise, and a drug capable of dealing with them may be necessary in order to save life.

Advantages of erythromycin are ease of administration, which is usually oral, although the intravenous route can be used if necessary, and freedom from toxic effects, other than gastric disturbance from large doses. Although some of the bowel flora, including clostridia, are suppressed, coliform bacilli are insensitive and hence unaffected, and the enteritis sometimes caused by aureomycin and terramycin has not been seen. One minor disadvantage is that according to most authors[4 5] only low concentrations are attained in the cerebrospinal fluid, and a failure in the treatment of pneumococcal meningitis with subsequent rescue by penicillin has recently been recorded.[6]

The outstanding weakness of erythromycin is the ease with which bacterial resistance to it can be acquired, a property which is illustrated in Dr. D. Hobson's study of the drug published at page 236 of this issue. This change occurs more rapidly than with any other antibiotic except streptomycin, and has been shown to be the cause of failure in the treatment of infections which do not respond readily to treatment, particularly bacterial endocarditis. In the experience of Haight and Finland[7] staphylococci isolated from the blood of two unsuccessfully treated cases of acute endocarditis had increased in resistance 32- and 250-fold. The results of treating subacute bacterial endocarditis have also been in general unfavourable, although there is some suggestion that erythromycin may be indicated in combination with streptomycin or bacitracin for infections resistant to penicillin.

How should a drug with these properties be regarded in the present situation of antibiotic therapy? Its novelty and efficacy in a wide range of conditions will in the ordinary course of events

[1] See report in the *British Medical Journal*, 1953, **2**, 1043.
[2] Needham, G. M., and Nichols, D. R., *J. Lab. clin. Med.*, 1953, **41**, 150.
[3] Kirby, W. M. M., and Ahern, J. J., *Antibiot. and Chemother.*, 1953, **3**, 831.
[4] Haight, T. H., and Finland, M., *Proc. Soc. exp. Biol. (N.Y.)*, 1952, **81**, 175.
[5] Smith, J. W., Dyke, R. W., and Griffith, R. S., *J. Amer. med. Ass.*, 1953, **151**, 805.
[6] Grigsby, M. E., Johnson, J. B., and Simmons, G. W., *Antibiot. and Chemother.*, 1953, **3**, 1029.
[7] *Proc. Soc. exp. Biol. (N.Y.)*, 1952, **81**, 183.
[8] Martin, W. J., Nichols, D. R., and Geraci, J. E., *Proc. Mayo Clin.*, 1953, **28**, 609.

promote extensive use. Some authors in the United States appear to regard this with complacency, others with alarm. The following assessment of the position from the Mayo Clinic typifies the second of these viewpoints.[8]

"We wish to emphasize that we do not advocate use of erythromycin against chronic infections such as osteomyelitis, bacterial endocarditis and the like, because of the strong likelihood of provoking bacterial resistance. For the same reason we abhor the indiscriminate use of the substance, especially in those instances in which sufficient bacteriologic data are not accumulated to indicate the need for erythromycin. A strain of *M. pyogenes* (staphylococcus) carelessly made resistant to erythromycin in one patient may conceivably provide the basis for lethal cross-infection of another patient. We are especially fearful that ointments which contain erythromycin may rapidly increase the incidence of resistant strains of bacteria."

This warning from an authoritative source should not go unheeded. Intelligently and selectively used, this drug will be an invaluable resource for many seriously ill patients for years to come. Prescribed in half-hearted doses for trivial conditions or used in ineffective ways in the treatment of chronic sepsis, it will breed a race of bacteria, particularly staphylococci, against which we may have no further defence.

POST-OPERATIVE POTASSIUM DEFICIENCY

In his Harveian Oration for 1953, which appears in our opening pages this week, Dr. George Graham concludes the part on post-operative intravenous replacement therapy with the following words:

"During the period after operation, when the serum potassium may be high, it is necessary to steer away from the Scylla of hyperpotassaemia and towards Charybdis, using plenty of water, salt, and glucose, but as soon as the danger of being wrecked on Scylla is passed, and Charybdis with its low serum potassium and ileal stasis is being neared, the helm must be put over for Scylla, using water, potassium, and glucose, and either greatly reducing or omitting the sodium altogether."

Recently there have been a number of reports suggesting that potassium depletion is responsible for the occurrence of paralytic ileus after surgical operations,[1-5] since intestinal motility is dramatically restored by the administration of potassium salts. In the past paralytic ileus has been shown to respond to several different measures, such as treatment with a high protein intake[6] and with hypertonic saline,[7] to name only two. In view of this, and since potassium depletion is an ineluctable feature of the normal response of the body to surgical trauma, it would be interesting to know the incidence of paralytic ileus after operations of comparable severity and duration on parts of the body other than the gastro-intestinal tract and abdomen. If this turned out to be significantly less than the incidence after abdominal operations, that might imply that other factors, such as handling of the intestine, peritonitis, or tension on the pelvic floor, may also play their part in inducing ileus. Furthermore, post-operative potassium deficiency is only one aspect of a general metabolic upset affecting every constituent of the internal environment, and possibly it is the physico-chemical conditions which result from the general disturbance, rather than from that of one ion alone, which are responsible for symptoms.

This is not to say that potassium depletion is without danger, but it should not exclusively command attention. Its clinical manifestations, other than paralytic ileus, are rarely encountered, even when unequivocal evidence of the depletion exists.[8] The most commonly occurring symptoms ascribed to it in one group of cases were apathy and listlessness.[9] Yet Moore[10] regards these as manifestations of the "adrenergic-corticoid" phase of the normal metabolic response of the body to surgery. In experimental depletion induced in healthy subjects no symptoms were experienced,[11] though another group of workers, when the depletion was accompanied by acidosis, found lethargy, difficulty in concentrating, and absentmindedness.[12] Although microscopic lesions of the myocardium have been reported at necropsy on cases of long-standing potassium depletion,[13-15] and the abnormalities of the electrocardiogram associated with the condition are well known,[16 17] Clark[18] showed that the frog's heart could continue to beat even after losing half its potassium content so long as there was a trace of potassium present in the infusion fluid; and

1 Ebrill, D., and Naftalin, L., *Lancet*, 1953, **2**, 411.
2 Logan, J. S., *British Medical Journal*, 1953, **2**, 532.
3 Randall, H. T., *et al.*, *Surgery*, 1949, **26**, 341.
4 Richardson, J. E., *et al.*, *Lancet*, 1953, **2**, 587.
5 Streeten, D. H. P., and Ward-McQuaid, J. N., *British Medical Journal*, 1952, **2**, 587.
6 Ariel, I., *et al.*, *J. Amer. med. Ass.*, 1943, **123**, 28.
7 Ochsner, A., *et al.*, *Arch. Surg., Chicago*, 1933, **27**, 742.
8 Tarail R., *et al.*, *J. clin. Invest.*, 1952, **31**, 23.
9 Eliel, L. P., *et al.*, *New Engl. J. Med.*, 1950, **243**, 471 and 518.
10 Moore, F., *Ann. Surg.*, 1953, **137**, 289.
11 Black, D. A. K., and Milne, M. D., *Clin. Sci.*, 1952, **11**, 397.
12 Fourman, P., and Ainley Walker, K. M. S., *Lancet*, 1952, **2**, 368.
13 Keye, J. D., *Circulation*, 1952, **5**, 766.
14 Perkins, J. G., *et al.*, *Amer. J. Med.*, 1950, **8**, 115.
15 Rodriguez, C. E., *et al.*, *Amer. J. clin. Path.*, 1950, **20**, 1050.
16 Bellet S., *et al.*, *Amer. J. Med.*, 1949, **6**, 712.
17 Howard, J. E., and Carey R. A., *J. clin. Endocr.*, 1949, **9**, 691.
18 Clark, A. J., *The Metabolism of the Frog's Heart*. London. 1938.
19 Heppel, L. A., *Amer. J. Physiol.*, 1940, **128**, 440.
20 Black, D. A. K., *Lancet*, 1953, **1**, 353.
21 Aikawa, J. K., and Fells, J. H., *Amer. J. Med.*, 1952, **13**, 640.
22 Merivale, W. H. H., *Practitioner*, 1953, **171**, 267.
23 Elkinton, J. R., *et al.*, *J. clin. Invest.*, 1948, **27**, 74.

Heppel[19] found that the muscle cells of potassium-depleted rats were still able to contract even though half the intracellular potassium was replaced by sodium. Black[20] believes that a depletion of 250–300 mEq is unlikely to be accompanied by symptoms in human beings, and another group of workers[21] found that no symptoms occurred with depletion of about 30% of the body potassium. The conclusion seems to be that nearly all surgical patients suffer from mild symptom-free potassium depletion, which they soon repair for themselves by an early return to natural feeding. Symptoms arise only when the depletion is of long duration, as happens with surgical patients who are unable to resume oral feeding soon after operation, and in whom the normal post-operative loss of potassium is aggravated either before or after operation by loss of gastro-intestinal contents from vomiting or diarrhoea, by acidosis, or by the infusion of large amounts of sodium.

Patients with potassium depletion lie very still in bed, their faces slack and immobile with eyelids half-closed. They move slowly and with effort and speak in a whisper, but at this stage are not paralysed, though if left untreated they may pass into paralysis. They often say voluntarily that they feel very tired, and, rarely, they complain of aching in the leg muscles. Apart from the apathy, which seems to be imposed as much by their physical weakness as by any direct effect of the depletion on the brain, their minds are clear. In cases of long-standing and profound depletion, mental confusion passing into delusional excitement may occur, but this is unusual. The electrocardiographic signs of potassium depletion which have been reported[16 17] are not invariably elicited even in cases of long-standing depletion and very low plasma potassium concentration, but should be looked for.

Chemically, a low plasma potassium concentration helps to clinch the diagnosis. But the plasma potassium concentration is simply the balance between the leakage of potassium from the cells into the plasma and the drain of the kidneys from it. If excretion by the kidneys is poor, the cells may have poured out enough of the ion to keep the plasma concentration high or normal, even though there is a considerable intracellular deficiency. Nevertheless the unequivocal clinical symptoms of potassium deficiency are rarely seen when the plasma potassium concentration is more than 3 mEq per litre. Hypochloraemic alkalosis, which is wholly or partly resistant to treatment with sodium chloride infusions, may also occur, and should suggest the possibility of potassium depletion.

In most surgical cases treatment with potassium salts should be deferred until the patient can resume normal feeding by mouth. There are a number of reasonably palatable milk drinks and meat extracts which are specially rich in the ion,[22] and these can be used to supply, even in early post-operative convalescence, 100 mEq of potassium a day. Those who undertake intravenous replacement with potassium would do well to realize, like King Canute, that they cannot compel the tides of the internal environment, but can only supply the ion in appropriate amounts to the extracellular fluid, where excess of it may be lethal. Its subsequent distribution is probably dictated by the metabolic activities and energy expenditure of the cells rather than by passive transfers resulting from differential permeabilities of cell membranes.[23] In fact, potassium therapy carries a definite risk[20] and should not be undertaken on all surgical patients as a routine. Only when a patient shows unequivocal clinical and biochemical signs of potassium depletion should potassium salts be given intravenously. Furthermore, since most of these patients are also suffering from sodium and water depletion, with the attendant effects on renal function, these should be corrected before attempting to repair the potassium deficiency. In other words, before intravenous potassium administration is undertaken there must be a good output of urine and the blood urea level must be within normal limits. Only if all these requirements are satisfied may intravenous treatment be given.

Replacement solutions of potassium should contain about 30 mEq and not more than 40 mEq of potassium per litre, as the chloride, phosphate, or lactate,[20] and are best given with 5% dextrose to encourage the migration of the ion into the cells. Potassium salts should not be infused at more than 40 mEq in three hours,[20] and the plasma potassium must be estimated daily, or more often if necessary, by a method capable of giving the result quickly, which in practice means the use of a flame-photometer. The amount of potassium needed to repair the deficit cannot be calculated as precisely as that of sodium in a case of sodium depletion. Usually, large amounts are needed, although symptoms often disappear after surprisingly little potassium has been given.[4] Intravenous administration must be stopped as soon as the patient can be fed by mouth. Finally, it would be unfortunate if emphasis on the importance of the part played by lack of potassium in the post-operative period were to obscure the fact that patients at this time are in an abnormal metabolic state and present problems in general nutrition of which potassium deficiency is only one.

VARIATION IN HUMAN MILK

Infant feeding is often a source of worry to the family doctor, and, although feeding troubles are more common in artificially fed infants, everyone with experience of general practice knows that breast-feeding is by no means always free of them. Yet it is considered to be such a natural process, and the product so constant and uniformly adequate and satisfying, that the difficulties and inconstancies associated with it have perhaps received insufficient attention. Why do some mothers with apparently well-developed breasts and an abundant milk supply fail to satisfy their infants? Why do others feed one baby successfully and fail with the next or a subsequent one? What is the particular value of colostrum?

Colostrum has long been recognized as of different composition from mature milk, and great interest has been aroused by the possibility that the infant may absorb immune bodies in it, but its composition and day-to-day variation have not been much investigated. In general, mature milk has been accepted as a fairly constant product containing about 2% of protein, 6–7% of lactose, and 3–4% of fat. That it varies in volume is appreciated, as are the facts that the first feed in the morning is the biggest of the day and that worry or exercise may diminish the flow, but variations in the constituents of the milk at individual feeds and from day to day have not been considered important. Test weighing has generally been the method used in practice to determine the efficiency of breast-feeding, and it is often said that if the infant receives 2½ oz. per pound body weight per day (165 ml. per kg.) he is getting sufficient—without thought of the composition of the milk. The generalization is often made, too, that if an infant is not thriving on breast milk he is unlikely to do better on an artificial feed. There has rightly been much propaganda for breast-feeding, for breast-fed infants are better specimens, withstanding infections better, and, when they do get infections, recovering more quickly. It is difficult to reproduce the intestinal flora found in breast-milk stools with any modification of cow's milk, and this flora is of importance in vitamin synthesis and perhaps also in the production of a growth factor. The end products of protein and fat digestion of cow's milk are different from those of human milk, and the digestive processes are understandably not as complete. Furthermore, any organisms found in normal breast milk are harmless, but great care has to be exercised in the sterilization of cow's milk to ensure constant freedom from harmful bacteria. But it is well to pause from time to time and examine our basic reasoning for this propaganda for natural feeding. Difficulties in breast-feeding do occur, and not all breast-fed infants are satisfactory in their progress. The reasons for this should be considered.

In a timely series of papers published in this and last week's issues of the *Journal* Dr. F. E. Hytten has drawn attention to the many variations in human breasts and their secretions. His carefully controlled experiments show that in any investigation it is necessary to collect the complete 24-hours milk output, and the mechanism of removing the milk is of great importance if errors are to be avoided. It is not always possible to empty the breasts completely by manual expression, but the use of an electric breast pump gives the maximum yield without disturbing the normal processes of secretion and production. With regard to variations in fat, lactose, and protein during any individual feed, Dr. Hytten confirmed that the fat increased as the feed proceeded and that the sugar decreased. By an ingenious mechanical device he showed that the most likely explanation for the progressive rise in fat was simply the mechanical adsorption of the fat globules on to the secretory and duct surfaces; the change in sugar and protein was probably secondary to the change in fat concentration, though the variation in the protein depended also on the maturity of the milk. In addition to these individual feed variations there is also a diurnal variation, both in quantity and particularly in fat content. Hytten's findings suggest that the volume changes are due not only to the interval between feeds but also to the storage capacity of the breast. He did not find any evidence that there was a constant secretion rate of milk, or that individual variations were due to any genetic influence. Another interesting finding was that milk produced in large volume (and therefore the most likely to find its way to a milk bank) generally had a high carbohydrate and low protein content. Hytten estimated that some 20% of women will have less than 3 g. of fat per 100 ml. in their milk and that it will have a caloric value of less than 570 per litre. It will therefore be incapable of adequately nourishing an infant after he has attained a weight of 11 lb. (5 kg.). Whether such poor milk can be enriched by changes in the mother's diet remains to be seen.

What practical conclusions can be drawn from Hytten's work? Human milk is not a static or constant product; it varies from day to day—and from feed to feed perhaps—both in volume and composition, and if an infant is not gaining satisfactorily the explanation should be sought promptly.

First, the possibility of infection or of constitutional disturbance should be considered. Either of these is, in general, more likely to be responsible than faulty or insufficient maternal milk. But if no such evidence is found additions to the diet in the form of complementary feeds should be given. In view of the marked variations in human milk, which are without any ill effect on the infant's digestive tract, it seems illogical to insist on the need for a completely standard composition for artificial feeds; they might well vary as much as human milk without any detriment. So long as the milk offered is of adequate caloric value, clean, and digestible, and contains a sufficient amount of protein and carbohydrate and is supported by vitamin supplements, strict insistence on the exact composition of the formula is not of first importance. Few general practitioners will have the facilities available for examination of the mother's milk and may well be in doubt both about the total volume secreted and about the infant's caloric intake over 24 hours. Common sense must prevail in infant feeding, as in every other branch of medicine, and the decision to wean an infant, or to give complementary feeds, must be made at the doctor's discretion, with the infant's general condition and progress in mind above all else.

TEETHING POWDERS

Purging the newborn has been a traditional custom for many centuries, inspired perhaps by a desire to rid the infant of inborn evil spirits. So long ago as 1748 Cadogan objected to this practice, complaining that nurses "often do much harm where they intend to do good, by fancying Nature has left a great deal to their Skill and Contrivance." But in the nineteenth century and up to the present day various purgative mixtures have found a ready sale to the public as "teething powders," and countless millions have been forced down the throats of helpless infants. Indeed, mothers often give the powders to children of all ages as a laxative regardless of the claim that they assist teething. Others have confined themselves to giving one when the child is fretful "to soothe it" or "to cool the blood," but many give a regular dose as a kind of charm to ward off unknown hazards ahead. It has even been known for a mother to dip her finger in the powder and rub her baby's gums with it. Grandmothers impress upon their daughters the value of such remedies just as their mothers had done before them, and the popularity of these products has been maintained, against all medical progress, for over a century.

In recent years opinion has been growing among paediatricians not only that such powders are ineffective but that they have been dangerous also. The mercury in them has been incriminated as an important aetiological factor in pink disease and also in some cases of nephrosis.[1] Dr. J. G. Dathan shows in a paper at page 247 of this issue of the *Journal* how dangerous they may be. It is not certain whether other factors are involved in the causation of pink disease (many have been postulated), but there will be a good opportunity for investigating the residual cases which occur after the present supplies of powders containing calomel have disappeared from the chemists' shops—provided all concerned follow the lead already given by one manufacturer in marketing these powders without calomel in future. If they fail in what is now their obvious duty, Parliament will no doubt intervene immediately, and it is to be hoped that there will be no need for the legal prohibition sought by Mr. S. T. Swingler, M.P., on January 21.[2] It would be as well also for doctors to refrain from prescribing grey powders for such conditions as jaundice, skin rashes, or gastro-enteritis, for which calomel has been a time-honoured remedy.

In paediatrics the aim should be to interfere as little as possible with the course of nature where normal processes are concerned. Non-interference is now recommended for many aspects of the care and management of the newborn; thus, the premature baby is left undisturbed for several days after delivery, the ritual of frequent bathing and vigorous cleaning of the mouth and eyes has been curtailed, restrictions on the time and quantity of feeds have been relaxed, unnecessary operations for tongue-tie and "phimosis" are in disrepute, and complicated orthopaedic measures for straightening the natural curves of the lower limbs are happily being abandoned so that spontaneous recovery (if indeed that is the right word) may take place unaided. A worthwhile task for family doctors is to do all they can to discourage mothers from the routine administration of unnecessary medicaments to their offspring. At present about 75% give gripe-water and teething powders from the second month of life, incidentally thus initiating from the outset the bottle-of-medicine habit which is no credit to the N.H.S. Gallons of gripe water are given to young babies for the wind, but often unsatisfied hunger is the cause of the crying and more milk the appropriate remedy. Gripe water usually contains sodium bicarbonate, which gives off carbon dioxide when it reacts with the acid gastric contents; burping results, and its efficacy is plain for all to see. Teething powders seem likely to contain phenolphthalein in the future, so that their purgative action will be maintained, and mothers will presumably still be calmed by the fact that something is being done. Nevertheless teeth will continue to erupt at their own rate with or without causing symptoms and completely unaffected by any form of therapy.

UTERO-TUBAL INSUFFLATION

The procedure of utero-tubal insufflation will always be associated with the name of Rubin, who introduced it into gynaecological practice over 30 years ago and recently devoted a book to his long experience with it.[1] In this issue of the *Journal* (p. 239) Dr. Albert Sharman

[1] *British Medical Journal*, 1953, **2**, 1317.
[2] See Medical Notes in Parliament, p. 281.

retails some of the lessons he has learnt from performing over 4,000 tests. He follows Rubin in advising the use of carbon dioxide as the test gas because no fatal case of air embolism or of pelvic infection has been reported from its use, whereas fatalities from these complications have occurred after the use of air and oxygen. Carbon dioxide is unquestionably the safest gas, but some gynaecologists remain satisfied with the careful use of air, for it requires only the simplest apparatus, an advantage of some importance if the test is to be performed in consulting-room or out-patient department. If the Bonney insufflator with a bulb without a valve is used, and if the capacity of the bulb, about 45 ml., is not exceeded, the risk of fatal embolism is almost obviated. Whatever gas is used, insufflation very rarely introduces infection into the genital tract; any reaction is almost invariably a recrudescence of an old infection, and, if severe, should raise the suspicion that genital tuberculosis is present. Tubal patency tests should be avoided if there is any acute or chronic vaginal discharge, if menstruation is imminent, in progress, or overdue, or if a previous test has caused a reaction; but, if a history of old pelvic infection is regarded as a contraindication, the test will be omitted when the information it may give is most needed.

It is generally realized that tubal patency tests can give false or misleading results, and White[2] has detailed some of the reasons, but the extent of their fallibility is often not appreciated. Dr. Sharman found that, of 102 consecutive women with negative tests, a further testing a few days later showed normal patency in 70. In a paper read at the 1953 Annual Conference of the Society for the Study of Fertility, Jeffcoate reported that 37% of negative insufflation tests were subsequently proved false by salpingography, laparotomy, or pregnancy. The proved false positive rate was much lower, about 3%. Dr. Sharman recommends that salpingography should be performed in all cases diagnosed as non-patent by insufflation. This complementary procedure more than halves the rate of proved error but does not obviate it; and indeed Jeffcoate found that even when both tests were negative the margin of error was 15%.

It might be argued therefore that, if only in the interests of accuracy, salpingography should replace insufflation as a diagnostic measure, but it is unlikely to do so for three reasons. First, insufflation is simpler, cheaper, safer, and more easily combined with other procedures such as endometrial biopsy. Secondly, many gynaecologists have implicit faith in kymography as an adjunct to insufflation. Dr. Sharman, like Rubin,[3] believes that the kymograph enables the observer to distinguish not only between patency and non-patency but also between tubes which are normally patent and those which are the site of spasm, stenosis, or peritubal adhesions. This belief presupposes that the oscillations of the recording needle are produced by tubal contractions and that these accurately reflect tubal health. These two assumptions may not be accepted unreservedly, especially by those who have performed insufflation with kymography when the tubes are under direct vision at laparotomy. The third reason for retaining insufflation is that, whether the test proves positive or negative, if the patient does not become pregnant within six or twelve months thereafter, a different test, salpingography, can then be performed. If one tubal patency test can have a therapeutic value, how much more valuable are two, suitably spaced, for in the treatment of infertility time is a powerful ally for success on the side of the gynaecologist.[4]

1 Rubin, I. C., *Utero-tubal Insufflation*. Mosby. St. Louis. 1947.
2 White, M. M. *J. Obstet. Gynaec. Brit. Emp.*, 1951, **58**, 573.
3 Rubin, I. C., *Fertil. and Steril.*, 1952 **3**, 179.
4 Bender, S., *British Medical Journal*, 1952, **2**, 409.

GROUP PRACTICE ENCOURAGED

One of the recommendations of the Working Party on the Distribution of Remuneration among General Practitioners[5] was that a provisional sum of £100,000 should be set aside annually to be used to encourage the formation of group partnership practices. Now, after consultation with the General Medical Services Committee of the Association, the Minister has decided that this money should be used to provide interest-free loans to those "general practitioners taking part in general medical service who propose to form a group practice or who, having formed a group, propose to provide new practice premises or substantially to improve the existing premises" (see *Supplement*, p. 27).

The last reports of the Medical Practices Committees of England and Wales[6] and of Scotland[7] show that the Working Party's recommendations about the loading of capitation fees and the fact that partnerships can gain the maximum advantage from this loading by arranging to be paid on notional lists have already done much towards increasing the number of partnerships. The Minister's decision to assist capital expenditure on premises for group practice purposes should help further to increase this trend by removing what has been, in some cases at all events, an obstacle to expansion.

Inquiries made by the B.M.A.'s General Practice Review Committee[8] showed that enthusiasm for health centres was lukewarm and that fewer G.P.s were in favour of them than were against them. The Committee thought it preferable that any changes in the form of general practice should develop spontaneously from within practice itself rather than from the imposition from outside of some organization such as health centres. Certainly general practitioners have been showing an increasing interest of recent years in the advantages attached to group practice, and the Minister's proposals will give practical encouragement in a way which should be acceptable.

The annual sum of £100,000 for loans will be swollen in due course by repayments until eventually much more capital will be available. The favourable terms are likely to stimulate inquiry from many doctors into the possibilities of group practice, and at first the Group Practices Loans Committee—to be composed equally of G.P.s and Ministry officials—may well find their resources unequal to the demand on them.

5 *British Medical Journal Supplement*, 1952, **1**, 283.
6 Ibid., 1953, **1**, 74.
7 Ibid., 1954, **1**, 9.
8 Ibid., 1953, **2**, 131.

CLINICAL PATHOLOGY IN GENERAL PRACTICE

THE LABORATORY DIAGNOSIS OF PULMONARY TUBERCULOSIS

BY

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In any case of pulmonary tuberculosis the laboratory has two important roles to fulfil. First, it plays an essential part in the diagnosis; for until *Mycobacterium tuberculosis* has been demonstrated in exudate or tissues of a patient the diagnosis remains incomplete. Secondly, the laboratory has an important function to fulfil in the control of treatment. This paper is concerned only with the diagnosis of pulmonary tuberculosis. Nevertheless, at the stage of diagnosis there are certain steps which should be taken if the laboratory is to exercise its function in the control of treatment. These steps are mentioned in the course of the paper. The essential step in diagnosis is the demonstration of tubercle bacilli, and consideration is given first to the various tests that may be employed for this purpose. Later, their application to specific excretions or tissues is discussed.

Microscopical Detection of Acid-fast Bacilli

This is the most widely employed laboratory investigation in tuberculosis and has the great merit of speed. A report on the presence or absence of acid-fast bacilli in a given specimen is available in a few hours.

Unfortunately, there is no method of differentiating between *Myco. tuberculosis* and non-pathogenic acid-fast saprophytes under the microscope. Mycobacteria are, by definition, a group of bacteria which, when stained, resist decolorization with acid and alcohol. Since 1894, the Ziehl–Neelsen technique has been the accepted standard procedure all over the world. In this method the bacilli on the film are stained with carbol-fuchsin, decolorized with acid and alcohol, and counter-stained with methylene blue. The acid-fast bacilli thus appear under the microscope as red rods against a blue background, as viewed by reflected light. Recently a new technique has been developed whereby the acid-fast bacilli are stained by fluorescent dyes, decolorized in the normal way by acid and alcohol, and counter-stained. The stained bacilli, when irradiated by ultra-violet light, have the property of emitting visual light. This makes them appear larger and more easily seen under the microscope. While this new technique is a big advance from the laboratory point of view, it is essential to remember that it does not constitute a new development and that the property of acid-fastness is still the property which is recognized by both procedures.

Cultural Methods

Myco. tuberculosis is a slow-growing organism. Even when seeded on a culture medium favourable to its growth an inoculum containing viable tubercle bacilli may take from two to eight or more weeks to produce a recognizable colony. The length of time taken depends upon the number of viable bacilli in the inoculum, the smaller the number the longer the time. Obviously, if other bacteria are present in the material to be examined, these will overgrow the whole surface of the culture medium and will swamp the *Myco. tuberculosis*. It is therefore necessary to kill off the other bacteria in the specimen before inoculating it on to culture medium. It is also desirable to concentrate as many as possible of the viable tubercle bacilli from the whole specimen into a small volume, for the larger the number of bacilli used the quicker the growth will become evident. Fortunately, mycobacteria are far more resistant to the action of acids and alkalis than other bacteria, and the most satisfactory methods of concentration are based on this difference. It must be remembered that in a grossly contaminated specimen with much pus and secondary infection the amount of exposure to acid or alkali which is necessary to kill the secondary organisms in the specimen may also kill the majority of tubercle bacilli in that specimen. Therefore such specimens are apt to give false-negative results.

Animal Inoculation

Until the development of modern egg media, animal inoculation was a much more sensitive method of detecting *Myco. tuberculosis* than culture. From the large number of investigations which have been performed to compare the relative merits of the two methods, it is clear that cultures are now as sensitive as animal inoculation, and the high cost of the latter would prohibit a high proportion of the investigations now usefully performed by culture. In material in which contamination by acid-fast saprophytes is likely, as in specimens of urine, and in which typing of the strain is required, animal inoculation is still the method of choice. Indeed, the usefulness of animal inoculation is now very limited, and cultural methods on the more normally submitted material are every bit as accurate.

Pathological Material

These standard methods of investigation must now be considered in relation to the pathological material which is available for diagnosis in cases of pulmonary tuberculosis.

Sputum

The material most often examined in cases of suspected or proved pulmonary tuberculosis is undoubtedly sputum. The specimen should contain little saliva and be free from food particles. The early morning, before breakfast, is the best time to collect such a specimen and the patient should be provided with a clean, dry, wide-mouthed sterile container. If the disease has not previously been diagnosed the specimen should be examined by a direct film for microscopy, and whatever the result the specimen should be concentrated and cultured for *Myco. tuberculosis*. Unless the first specimen shows many acid-fast bacilli in the direct film, it should be followed by two further specimens, which will also be put up for culture if the diagnosis of pulmonary tuberculosis is regarded as likely on clinical grounds. If these three specimens prove negative on microscopy it will be necessary to repeat the test at frequent intervals until either a positive result is obtained or some diagnosis other than tuberculosis is established. In any event, the wisest course at this stage is to persist in cultures until a positive result is obtained, especially if there is any likelihood that chemotherapy will be instituted or any possibility that the patient has contracted the disease from a patient who has been treated with streptomycin.

Gastric Lavage

The stomach washings are useful material from which to cultivate *Myco. tuberculosis* in patients with pulmonary tuberculosis who fail to expectorate.

The specimen should be taken before breakfast and there should be no delay in submitting it to the laboratory. It must be remembered that the gastric juice is strongly acid and if the specimen is left unneutralized for more

than one hour it is probable that the tubercle bacilli will be killed. To the gastric washings 5 ml. of 10% trisodium-phosphate should be added to neutralize the acid. The presence of acid-fast bacilli in a smear made from the gastric contents is not conclusive evidence of the presence of *Myco. tuberculosis*. Many foodstuffs, notably butter, are often contaminated with saprophytic acid-fast bacilli. It is therefore essential to culture all specimens of gastric contents.

Laryngeal Swab

Gastric lavage is often difficult and usually impossible in general practice, and to meet this situation with patients who do not expectorate the technique of a laryngeal swab has been developed. A sterile swab, moistened with sterile water, is passed with the aid of a laryngeal mirror into the larynx. The patient then coughs, and any sputum in the upper part of the bronchial tree will adhere to the swab. This swab is treated with 10% sulphuric acid for five minutes, and then placed in 2% sodium hydroxide for a further five minutes. It is then inoculated on to Löwenstein–Jensen medium and incubated in the ordinary way. Nassau* obtained a positive swab from 44% of 273 sanatorium patients who did not expectorate, and Forbes and his colleagues† showed that the results of laryngeal swabs were as reliable as gastric lavage in out-patients.

Faeces

In children the faeces may be investigated for the presence of *Myco. tuberculosis* in cases of pulmonary tuberculosis in preference or in addition to the gastric lavage. This method is also sometimes used in adults, but here the presence of large numbers of tubercle bacilli are more likely to indicate tuberculosis of the intestinal tract than pulmonary tuberculosis.

Pleural Fluids

Simple non-turbid pleural effusions, although most commonly of tuberculous aetiology, often contain only few tubercle bacilli. The probability of demonstrating *Myco. tuberculosis* is increasingly likely the larger the volume of fluid used. As these fluids often contain fibrinogen, an anticoagulant should be added—for example, 1 ml. of 20% sodium citrate. If possible about 100 ml. of fluid should be examined microscopically. If no organisms or only acid-fast bacilli are seen, six slopes of Löwenstein–Jensen medium may be inoculated. If other organisms are seen the material is used first for culture of secondary organisms and then treated by Petroff's or the trisodium-phosphate techniques before cultivation for *Myco. tuberculosis*. A small volume of the fluid should be examined for cells, and in simple tuberculous effusion the lymphocytes will predominate.

Turbid and purulent fluids should be treated in the same way, and in these cases there will be greater probability of successful cultivation.

One of these procedures will result in a positive culture from a case of pulmonary tuberculosis. With the widespread use of chemotherapeutic agents in treating tuberculosis, it is inevitable that some cases of pulmonary tuberculosis will be found in which the organisms are resistant to one or other of the chemotherapeutic agents. It is therefore necessary that the first culture from a new case of pulmonary tuberculosis should be preserved and preferably have its sensitivity tested against streptomycin, P.A.S., and isoniazid, as, even if not immediately, chemotherapy is very likely to be used sooner or later in the course of the patient's treatment.

The definitive diagnosis of pulmonary tuberculosis depends upon the demonstration of *Myco. tuberculosis* in the tissues or excretions. Nevertheless, there are other ancillary tests which, while not actually diagnostic of pulmonary tuberculosis, are of great assistance in estimating its severity and the course of treatment. These tests may be divided into the serological tests and the haematological tests.

* *Proc. roy. Soc. Med.*, 1941, **34**, 397.
† *Lancet*, 1948, **2**, 141.

Ancillary Investigations

Middlebrook and Dubos‡ showed that sheep's erythrocytes suitably activated with an extract of the strain *Myco. tuberculosis* H37Rv were agglutinated by the blood serum of some cases of pulmonary tuberculosis. Various other workers have made investigations along these lines, each of them making minor modifications in the technique. Sohier, for instance, used purified tuberculin to sensitize the red cells and obtained good results with tuberculous sera but had a high percentage of false-positive results in normal controls. While this relatively recent development may eventually prove satisfactory, there is at present no serological diagnostic test of proved value available.

Haematology

The most constant alteration in the blood picture in all forms of pulmonary tuberculosis is a progressive hypochromic anaemia. This usually reacts well to adequate treatment.

There have been many investigations into the changes in the total and differential leucocyte counts which may be associated with pulmonary tuberculosis. The only fact which emerges with certainty is that there is no specific change in the leucocyte count of diagnostic value. On the other hand, the disease may be associated with either a leucopenia or a moderate leucocytosis. There have also been reports of a leukaemoid reaction in a few cases of tuberculosis. The monocyte count is often raised (over 10%), especially when fresh tuberculous tissue is being formed, while a raised lymphocyte count is often associated with healing tuberculous lesions.

Erythrocyte Sedimentation Rate

Although the erythrocyte sedimentation rate is not in any way specific for tuberculosis, it is nevertheless of great value. In all toxic conditions associated with tissue destruction the sedimentation rate is raised, and thus the test is no more specific than pyrexia or leucocytosis. The sedimentation rate is always raised in active tuberculosis and falls as healing takes place. Serial examinations are thus of great value in the control of patients suffering from pulmonary tuberculosis, and a spread of the disease may manifest itself by a rise in the sedimentation rate before there is any radiological or clinical evidence of it. The test is also often valuable in cases in which radiographs reveal a lesion which is of doubtful activity, and in these cases a raised sedimentation rate is strong evidence of activity.

Westergren's method is commonly employed in tuberculosis. In this method 0.4 ml. of 3.8% citrate solution is drawn into a syringe which is then introduced into a vein. Blood is withdrawn until there is 2 ml. of mixed blood and citrate in the syringe. The sedimentation tube, which has an internal diameter of 2.5 mm. and is calibrated in millimetres from 0 to 200, is then filled in the manner of an ordinary 1-ml. pipette. The column of blood is drawn up to the zero mark on the scale and the tube is placed to stand vertically in a rack. At the end of one hour the number of millimetres through which the erythrocytes have sedimented is recorded. The disadvantage of the method lies in the fact that it is impossible to correct for anaemia, but the ease of the technique more than compensates for this somewhat technical disadvantage. It has been found in practice that serial readings of the sedimentation rate by the Westergren method are of very great assistance in controlling individual cases, and it is therefore always desirable to take a reading as early as possible in every case of pulmonary tuberculosis.

Next article on Clinical Pathology.—"The Normal Blood Count," by Dr. George Discombe.

‡ *J. exp. Med.*, 1948, **88**, 521.

THE MONTREAL GENERAL HOSPITAL

BY

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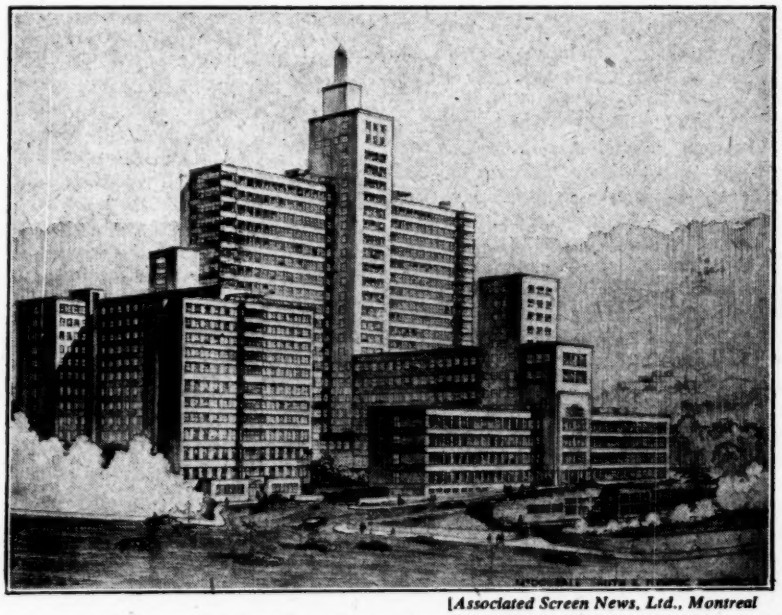
Great developments have taken place in Canada in the last decade, and with the large increase in population more hospital beds have become necessary. In the City of Montreal alone 3,000 hospital beds are being built at present to meet the demands of this rapidly expanding cosmopolitan city. The largest single hospital building project in Montreal, in fact in Canada, now being undertaken is the construction of the new buildings of the Montreal General Hospital.

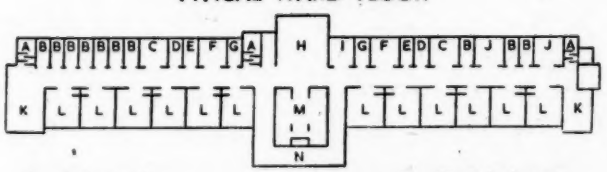


[Associated Screen News, Ltd., Montreal

FIG. 1.—Architect's drawing of the new buildings of the Montreal General Hospital.

The Montreal General Hospital, a teaching hospital of McGill University, was founded in 1821, and ranks as the oldest teaching hospital in Canada and one of the oldest on the North American continent. Founded by four Edinburgh graduates, it was built in the style of the Royal Infirmary of Edinburgh and throughout the years has maintained close ties with that city. In 1949 a survey of the hospital revealed that modernization of the present buildings would be impossible, and consequently it was decided to erect an entirely new hospital expanding from 640 beds to 750 beds. The hospital authorities were fortunate in securing an area of land of 360,000 sq. ft. (33,450 sq. metres) almost in the centre of the city and within easy reach of suburbs. On this site the new Montreal General Hospital is being erected and one-half of it has now been completed. The cost of the hospital amounts to $20m. (£7m. at the present rate of exchange). Two-thirds of this money has been obtained by public subscription, the remainder being provided by the Federal Government of Canada, the Government of the Province of Quebec, and the City of Montreal.

TYPICAL WARD FLOOR



A. Staircase
B. Single-bed room
C. Baths, flowers, etc.
D. Cleaning utility
E. Examination and treatment
F. Nurses' station
G. Doctor's office
H. Waiting-room
I. Seminar
J. 2-bed ward
K. Solarium
L. 4-bed ward
M. Elevators
N. Ward kitchen

Internal Design

When completed the hospital will have 750 beds and 50 bassinets and a nurses' home to accommodate 250 nurses. The design of the hospital is unusual, as can be seen from the drawing, with an out-patient wing housing full out-patient services, a dental teaching school, and a floor devoted to a psychiatric department with some 20 in-patient beds and 15 beds which will be used for psychiatric patients who receive treatment during the day and go home at night. These same beds will also be used for psychiatric patients who are working during the day and have their treatment at night. The connecting wing will house all the ancillary and diagnostic services, kitchens and staff dining-rooms, and operating suites. The remaining wing is devoted entirely to in-patients, each floor providing accommodation for 64 patients each with two nursing units of 32. In order to make the maximum use of beds and have as flexible a plan as possible no ward will contain more than four beds; private patients will be accommodated in single rooms and numerous single and two-bed rooms have been provided on the public patient-floors. The nurses' home and interns' home are both connected with the main hospital by tunnel, every nurse having her own room and toilet facilities.

All the ten operating-room suites are air-conditioned, and provision has been made for the installation of a cobalt bomb or million volt *x*-ray therapy machine. Oxygen will be piped to every bed. Automatic-pneumatic tubes will carry records, specimens, and drugs to thirty different outlets throughout the hospital, thus saving many man-working hours. It is hoped to install also a new "walkie-talkie" call system for interns, thus eliminating audible and visual call systems. Eight high-speed elevators are to fitted, with provision for additional elevators should the need arise.

An amphitheatre to seat 230 people has been provided for. This is in addition to the numerous small lecture theatres available throughout the hospital for the teaching of undergraduates and postgraduate medical men. Every patient-floor has a waiting-room, lecture room, and sun lounges; all patient rooms are equipped with a nurses' call system allowing the patient to talk to the nurse direct from the bed to the nurses' station.

On the domestic side, there is an automatic ice-making machine on every patient-floor. A laundry is to be installed to meet the needs of the whole hospital, with linen chutes on every floor to carry the dirty laundry. All windows will be of the double-hung reversible type to allow easy cleaning. Heating will be by means of oil furnaces, and an independent generator will be installed in case of main electrical breakdowns. The basement will provide food storage space for a minimum of six months' supply of non-perishable foods at any time. All preparation of meat and vegetables will be carried out in the basement, thus allowing more freedom of movement in the central kitchen on the fourth floor, which also houses three large staff dining-rooms.

It is thought the new Montreal General Hospital will be in operation by 1955. It will be the most modern teaching hospital on the North American Continent and its opening will be a great milestone in the history of medical and nursing teaching in Canada. It is hoped that many members of the British Medical Association when they visit Canada for the joint meeting with the Canadian Medical Association in 1955 will find time to visit this new hospital, which has such a strong tie with the Scottish and English medical schools.

ERYTHROMYCIN

Erythromycin in limited amounts has lately been made available by the Ministry of Health to hospitals in the National Health Service, and very shortly it will be freely available on prescription. The Ministry is therefore sending to all hospitals the following note by the Medical Research Council on its use.

Indications and Dangers

Erythromycin has a range of activity similar to that of penicillin and has been shown to be effective in acute infections due to haemolytic streptococci, pneumococci, and staphylococci. Organisms resistant to all other antibiotics are nevertheless sensitive to it: hence its greatest value is in treating staphylococcal infections not responsive to other drugs, the frequency of which, particularly in hospitals, is showing a disturbing increase. A peculiar form of this infection in which its action may be life-saving is the severe staphylococcal enteritis complicating therapy with the broad-spectrum antibiotics or with penicillin and streptomycin. Some other species, including members of the genera *Neisseria* and *Haemophilus* and *Rickettsia*, are also sensitive to it.

Erythromycin is itself a drug to which bacterial resistance can be acquired rather rapidly, and this may be a cause of treatment failure in infections difficult to eradicate, such as endocarditis. It has also to be remembered that bacteria rendered resistant in one patient may later cause infections in others which are insusceptible to the drug from the outset. It might be disastrous if a staphylococcal population were built up which was resistant to erythromycin as well as to earlier antibiotics. It is therefore most necessary that this drug should be prescribed with due regard to the risks of indiscriminate use. Penicillin should be preferred, on this ground—and, it may be added, that of economy—when it will serve equally well. Erythromycin should not be prescribed for most chronic conditions which respond poorly to it as compared with acute conditions—for trivial indications, or for those in which the bacterial cause is unknown.

ORDER OF ST. JOHN OF JERUSALEM

The *London Gazette* has announced the following promotions in, and appointments to, the Venerable Order of the Hospital of St. John of Jerusalem:

As Commanders (Brothers): Colonel F. A. Bearn, C.B.E., D.S.O., M.C., M.D., Major C. D. Donald, M.B., F.R.C.S., Mr. H. S. Taylor-Young, F.R C.S., and Drs. D. J. Johnson, M.B.E., J. A. L. Roberts, J. B. McKay, W. Bain, N. J. L. Rollason, F. W. Hebblethwaite, T. F. Briggs, O.B.E., T.D., J. F. C. du Toit, and the Hon. W. Nicol. *As Officers (Brothers):* Surgeon Captain E. J. Mockler, M.B., Major G. Brown, M.B., Messrs. H. I. Marriner, F.R.C.S., E. A. Malkin, F.R.C.S., and St. J. M. C. Birt, F.R.C.S., and Drs. G. G. W. Hay, C. L. Worthington, A. E. Pinniger, A. T. G. Thomas, W. R. A. Line, J. W. Silversides, A. M. Boyne, W. M. Dinwoodie, M. C. Cooper, M.C., C. Homi, J. A. R. Lavoipierre, J. S. Binning, E. F. Baines, W. G. McAfee, H. A. Johnson, R. C. Webster, J. M. de Ville-es-Offrans, M.B.E., and R. E. Anderson. *As Officer (Sister):* Dr. Marian Maxwell-Reekie. *As Serving Brothers:* Mr. H. B. Walker, M.C., F.R.C.S., and Drs. A. B. Wallace, J. C. K. Chilcott, F. H. Cleveland, W B. Boone, A. Burns, O.B.E., M.C., R. Cubitt, D. S. Chowdhary, T. H. McLeod, J. F. D. Boyd, D. W. Hendry, V. F. Tyndall, J. A. H. Goldacre, A. Stewart, C. T. Newnham, J. E. Hilton, A. Hamerton, J. G. Wilson, A. S. Boyd, W. B. Wishart, L. N. Gollan, and J. V. Vaughan. *As Associate Serving Brothers:* Drs. J. B. Solomon and S. Adler. *As Serving Sisters:* Drs. Betty M. White and Ruth Hull. *As Associate Serving Sister:* Dr. Ray Schauder.

Reports of Societies

THE MANAGEMENT OF THE ALCOHOLIC IN GENERAL PRACTICE

A meeting of the Section of General Practice of the Royal Society of Medicine on January 20 was devoted to a discussion on the management of the alcoholic in general practice. Dr. A. TALBOT ROGERS was in the chair.

Dr. J. YERBURY DENT, Editor of the *Journal of Addiction*, gave an account of alcoholic patients whom he had successfully treated with apomorphine. He used apomorphine by mouth in the treatment of 75% of the addicts who came to him, and he knew of nothing so satisfactory in removing the compulsion. An overdose could not easily be given by mouth. For the first 24 hours the patient might still have a craving for alcohol; if so, he should remain in bed; on the following day the craving was likely to be much less or even gone, but the treatment should be continued for three or four days. A more drastic treatment, with intramuscular injections of apomorphine, usually lasted for a week or ten days, and after it the patients returned to work immediately. Some might relapse, but these could and often did treat themselves successfully by mouth.

Dr. Dent then gave an account of one man who, although a publican, had been treated and had remained a total abstainer for eleven years. The publican then proposed to marry and his intended bride asked him to drink to their future happiness. He told her of his earlier craving and his fear of relapse, but she said, "Then I am not going to marry a coward." He drank one glass of sherry with her, and the next day he drank nearly a bottle of whisky, whereupon she threw him over, saying: "I am not going to marry a drunkard." The man had a second course of treatment and was now once more a total abstainer—and a bachelor.

Although there was an enormous literature on the subject of alcoholic addiction the general practitioner did little for his alcoholic patients. Practically nothing was to be found in the textbooks and little was done for the thousands of addicts and their families. The old idea that all troublesome drunkards should be dealt with by the police still obtained. It was not yet realized that addiction was a disease, however much the act of drunkenness might be considered a moral lapse. The general practitioner could do a great deal to help his patients, and the patient and his friends should bully the doctor, if necessary, into treating the condition seriously. Dr. Dent protested against alcoholic patients being handed over to the psychoanalyst, though he admitted that psychotherapy and psychology had their place in treatment.

The Role of Psychotherapy

Dr. J. A. HOBSON agreed that apomorphine was the most useful drug available for the treatment of alcoholism, but he did not agree with what he considered to be Dr. Dent's disparagement of psychotherapy. Probably Dr. Dent himself practised far more psychotherapy with his patients than he was aware of; he was interested in his patients as human beings and not as "cases." He was sure that "Dent without apomorphine would cure more alcoholics than would apomorphine without Dent."

Psychotherapy was something which general practitioners could practise. Many alcoholics coming to doctors were coerced by their relatives and consequently very suspicious and guarded in their demeanour. Unless the general practitioner could win their confidence he was likely to fail.

Accuracy in diagnosis was, of course, important and of great academic interest, but diagnostic history-taking should be postponed if there was any risk that it would antagonize the patient. Most alcoholic patients showed some psychological abnormality, but it was difficult to decide whether the alcoholism was secondary to a neurosis or the neurosis secondary to alcoholism; he thought the latter was more likely to be the case. Very frequently symptoms of anxiety and tension disappeared under treatment. Often, of course, the alcoholic, after he became teetotal, was left with some psychiatric symptoms, and in such cases then proper psychiatric treatment was given. The alcoholic presenting himself for treatment exhibited a sense of shame and failure, and was always on guard against moral accusations. A doctor who was himself an alcoholic had described his own state as an intense dislike of himself, his habits, his behaviour, his reactions to his friends, and imagined himself guilty of unspeakable infamies. An attempt must be made to combat the alcoholic's feeling of complete loneliness and extreme self-reproach. To this end it was preferable to treat alcoholics in groups of two or three at a time rather than in isolation. Fostering a group spirit was one of the ways in which Alcoholics Anonymous was of most help in reinforcing medical treatment.

Team-work

Dr. LINCOLN WILLIAMS pleaded for team-work in the treatment of alcoholism. To understand the alcoholic was to understand his needs. These could be summarized under several headings.

First came his physical needs. It was essential to eliminate organic disease and to repair the ravages of alcoholism by fortified vitamin therapy. Over the last 50 years medicine had concentrated almost entirely on physical treatment—gold cures, courses of atropine and strychnine, and the like—which enjoyed a fleeting reputation, afterwards to be discredited. Modern therapy was carried out by means of aversion conditioned-reflex treatment, using apomorphine and "antabuse" (tetraethylthiuram disulphide).

Then there was the need for a personality diagnosis. It was very important to understand what the patient was like before the onset of his excessive drinking. Was he fundamentally a normal person, or one suffering from neurosis, or had he a mental disorder, or was he a "bad hat" alcoholic with an underlying psychopathic personality? One often came across patients who suffered from a chronic tension state which demanded more and more alcohol to allay it. This type of person responded extremely well to subconvulsive electrostimulation which removed the tension.

Furthermore, the environmental needs of the alcoholic must be considered. His wife must be helped to understand that compulsive drinking is an illness and not a moral failure. Where desirable, contacts might also have to be made with his employer, for many alcoholics held responsible positions in industry and had many years of productive work ahead of them. The social needs of the alcoholic could be met by membership of a group, and here the speaker gave wholehearted support to the work of Alcoholics Anonymous.

Finally the spiritual needs of the alcoholic also called for attention. The effect of religious conversion was well known. The Church to-day showed complete readiness to work with doctors and Alcoholics Anonymous and all others towards the successful rehabilitation of the alcoholic sufferer.

Dr. E. P. SCOTT said that he was disappointed that they had been told so little about the cause of alcoholism, whether physical or psychological, and also about its sequelae.

Three members of Alcoholics Anonymous also contributed to the discussion. One of them said that he had for 22 years been a hard drinker, and he had since spent two years in association with Alcoholics Anonymous and had won through to sobriety. It was very important that members of that organization should work under medical superintendence. Alcoholics Anonymous consisted of men and women of every social grade who had learnt to live without alcohol and by their fellowship and sharing of experiences to help one another. Another member of the organization said that he was sure that the drinking of alcohol was due to a state of mind and not so much a physical urge.

Complications of Alcoholism

Dr. HOBSON, in replying on the discussion, said that to argue whether the cause of alcoholism was physical or psychological was a trick of language rather than a true dichotomy. As for the sequelae of alcoholism, he had been struck by the very low incidence of cirrhosis in alcoholic patients. He had not seen a case of cirrhosis of the liver in an alcoholic for four or five years. Nor had he seen cases of gout. A disease which was rather similar to gout was diabetes, and there was a high incidence of diabetes not only among alcoholics but among their friends. The complications he saw most frequently were peripheral neuritis and mental changes. With regard to the compulsive craving for alcohol, he mentioned one woman patient who had retrobulbar neuritis and was told that if she persisted in drinking alcohol she would go blind. Her reply was, "Even if I go blind I cannot give it up." In marked contrast with this were patients with tobacco amblyopia. One of these, who was addicted to excessive cigar smoking, gave up the habit at once on being given a similar warning.

Dr. DENT, also in reply, said that he had his doubts about the value of psychoanalysis in these cases, but he had no prejudice against psychotherapy. He had never suggested, however, in dealing with patients that he had an interest in their past. The past had to be forgotten so far as possible. He had seen several alcoholic patients with diabetes, but not a single case in nearly 20 years with cirrhosis of the liver.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Press Publicity

SIR,—As chairman of the Association of British Science Writers, I have been asked by our members to thank you for your tolerant and constructive leading article on "The Press and The Profession" (*Journal*, January 16, p. 141), and to tell Professor Ian Aird that we fully appreciate the circumstances which provoked his letter (p. 153).

No responsible journalist will defend or excuse the behaviour of certain newspaper men on that occasion. Such conduct (of the few) brings discredit on the press—except that when there is a matter of wide public interest, a "human story," like the case of the Siamese twins, there is no such entity as "the press," only a large number of competitive newspapers and competing representatives, each trying to secure an individual account or an exclusive picture. It would be an exaggeration to say that the jobs of those representatives depended upon getting the story, but it would be true to say that they would be unpopular with their news editors or picture editors if others got what they did not. Any newspaper (even the most dignified) likes a scoop, but every newspaper is aggrieved by a "miss." It is the proper function, therefore, of every journalist to get the information which his newspaper wants by fair means. But not by foul.

The question which Professor Aird raised and your leading article discussed was: What is "fair means" in terms of the medical profession, with its concern for the special relationship between patient and doctor and of the ethic of anonymity of both patient and doctor? The further question was raised of the proper understanding, and competent handling, of medical facts.

As to fair means: there must be proper channels of communication if the Hammersmith "scrum" is to be avoided, and these channels must be facilitative and not restrictive; the non-committal hand-out will satisfy neither the conscientious journalist nor the justifiable public interest. There must be access to information and to individuals competent to give that information and to answer those questions which give a newspaper the sense of getting its own story.

Anonymity is a more difficult problem. The medical profession has established its own code of ethics and its own stern attitude to self-advertisement. Perhaps journalists, like the public, do not quite understand why certain doctors when they attain eminence seem to be outside this ethic, and, while not directly encouraging publicity, do not exactly discourage it; or why it is wrong to give a doctor's name in ordinary circumstances but permissible to quote him when he writes to the medical journals; or why, in circumstances in which there is no obvious professional advantage, naming a doctor is regarded as "unfair competition." Historically, the discouragement of medical self-advertisement grew out of notorious abuses, and only the medical profession itself can re-assess its *mœurs* in these *autres temps*. One thing is obvious: in circumstances such as the Siamese twins case, anonymity cannot hold. With the greatest sympathy, I, for one, could not suggest how Professor Aird could have remained anonymous; he was a part, and a creditable part, of the human story.

On the question of the proper presentation of facts, most newspapers have medical correspondents, concerned with clinical affairs, and all the leading national newspapers have scientific correspondents. They are supposed to grasp, intelligently, the essentials and to have skill in their presentation. In normal instances (the Siamese twins case was abnormal, journalistically as well as medically) they would be dealing with a case. With access to facts and with guidance, they could be expected to treat the facts with proper respect. They would neither claim nor expect that there should be a protocol which would, to the exclusion of their fellow journalists, restrict to themselves the access either to information or to informants. They would, however, suggest (and the newspapers recognize it by employing them) that there are areas of specialized information which are best explored by specialized journalists.

The Association of British Science Writers, which has full members, academic members, and associates, includes in its full membership the science editors or science correspondents of all (except one) of the leading national newspapers. It is not a bread-and-butter organization. It was formed primarily to raise the standards of scientific writing and the status of scientific writers, and, while it is concerned to ensure professional facilities for its members, it offers in return the proper handling of facts and of those responsible for those facts.

Therefore, while the Association cannot speak for journalists in general, it can speak for its own responsible members and say that it welcomes the understanding attitude of the *British Medical Journal* and that it will do anything it can to promote a working relationship between the press and the profession.—I am, etc.,

London, W.1. RITCHIE CALDER.

SIR,—The letter from Professor Ian Aird (*Journal*, January 16, p. 153) and the accompanying leading article (p. 141) are timely and welcome. They illustrate a difficult and as yet untackled problem. Most doctors have a dread of newspaper journalists because of the frequent unforgivable distortions, inaccuracies, and inventions they create from incomplete information acquired by devious methods. But might not the self-protective, ostrich attitude on the part of the profession be responsible in part for the highly undesirable, albeit understandable, methods of getting a story by some journalists?

Newspapers, both local and national, play an important role in the relationship between the community and the profession. An unnecessarily large gap exists between the public and the medical services (as exemplified by general practice, local authority, and hospitals). The appointment of members of the lay public to hospital management committees was a step towards bridging this gap, but, as they are not necessarily representative of community groups with the responsibility it implies, their so-called "public opinion" is often very far from real current opinion and feeling. A case in point is the daily visiting of children in hospital. Most parents would like the opportunity, but they accept the rule of the individual hospitals where it is not allowed as though it were the law. We are told there is nothing to stop the individual writing and expressing his views to the management committee, but there is a natural reluctance to be a complainer or "agitator," particularly when individual doctors and nurses are being so kind to their child.

The medical services have been in isolation too long from the public for whom they are designed and out of whose money they are maintained. Both suffer by it. The public would appreciate and benefit from more information about the medical services; this might in turn increase the civic sense and active interest as well as indirectly increasing the number of potential nurses. The doctors might benefit by knowing in a more realistic way what the public thinks and feels on different community issues. The press could be a vital link in this chain. A selected member of the administrative staff or the group management committee, executive council, or local authority could be appointed press officer; through him all press information would be given. Regular meetings between him and the journalists would go a long way in eradicating the circumstances responsible for the unfortunate experience of Professor Aird, and at the same time be the means of raising the standard of medical news in our newspapers.—I am, etc.,

London, W.1. DAVID MORRIS.

Controlled Hypothermia

SIR,—It seems that more care should be taken by writers of leading articles and annotations in the *Journal* to acquaint themselves not only with the literature on the subject but also with the papers which quote this literature and which inspire leading articles.

In your leading article on "Hypothermia" (*Journal*, December 5, 1953, p. 1256) we and our colleagues are taken to task for failing to corroborate that chlorpromazine produces autonomic block. In our paper in the same issue (p. 1237) we referred to the work of Courvoisier *et al.*[1] to justify our approach, and your more recent annotation (*Journal*, January 9, p. 89) takes cognizance of this work but fails to withdraw the comments made in the leading article. In this annotation on "Chlorpromazine for Hypothermia," it is suggested that we subscribe to the view that chlorpromazine was a ganglion-blocking agent. The original wording which we and our colleagues deliberately employed was: "This latter (chlorpromazine) is known to be a profound depressor of autonomic activity (Courvoisier *et al.*)." Dundee *et al.* (*Journal*, December 5, 1953, p. 1244) have also shown that chlorpromazine is an inhibitor of shivering more effective than pethidine, but stated that it was not their "purpose . . . to consider the mode of action of these drugs. . . ." In no place in either of these articles was it suggested that this substance was ganglion-blocking. It has, in fact, been established in as yet unpublished animal experiments that ganglion-blocking agents are, as might be expected, ineffective in preventing shivering.—We are, etc.,

JOHN W. DUNDEE.
Liverpool, 7. T. CECIL GRAY.

REFERENCE

[1] *Arch. int. Pharmacodyn.*, 1953, **92**, 305.

***We referred this letter to the writer of the annotation "Chlorpromazine for Hypothermia," who writes as follows: "The annotation said that 'suppression of shivering by curare or other substances has nothing to do with autonomic or ganglion blockade.' Drs. Dundee and Gray, how-

ever, base their work on that of Courvoisier and her colleagues, and the second point in the Courvoisier summary is that chlorpromazine is a ganglion-blocking agent. While they may reject this action as explaining the fall of temperature, it is surely clear that when Drs. Dundee and Gray wrote the three first paragraphs which appeared on p. 1238 of the *British Medical Journal* for December 5, 1953, they were under the impression that the autonomic system maintains body temperature, and that block at some point of this system prevents recovery of normal temperature. They say : 'The technique which we describe is a combination of induced hypothermia and "artificial hibernation," wherein the lowered body temperature is obtained by surface cooling, the lytic cocktail being employed to eliminate the body's normal responses to cold . . . we prefer to call the technique "induced hypothermia with autonomic block."'

"Except that sympathetic fibres prevent loss of heat by causing vasoconstriction in the skin, the autonomic system is not responsible for maintaining body temperature."—ED., *B.M.J.*

Whither Anaesthesia ?

SIR,—Dr. C. Langton Hewer in his letter (*Journal*, January 2, p. 42) expresses as few others could what must surely be in the minds of a very large number of experienced anaesthetists. Before the advent of "induced" hypotension (it could never truthfully be called controlled) anaesthesia had arrived at a remarkable degree of safety and efficiency. Thiopentone, nitrous oxide and oxygen, carbon dioxide absorption, muscular relaxation with curare or gallamine triethiodide, and avoidance of anoxia by assisted or controlled respiration had all contributed to this satisfactory state of affairs, which, happily, still persists in the practice of a great many anaesthetists.

With the adoption of these modern but well-tried methods great benefits have resulted. Post-operative shock as we used to know it has been practically eliminated even though operations have become longer and more extensive and are frequently performed on those patients who were formerly regarded as very bad risks. Post-operative morbidity has been tremendously reduced. Bleeding, however, still goes on. The skilful surgeons cope with it skilfully, and most would agree that only in a minute fraction of cases can it prevent the proper performance of the operation or in any real way affect the prognosis. It seems a pity, therefore, that some anaesthetists have been led to employ techniques which expose their patients to risks which make those of shock and haemorrhage look insignificant by comparison. Some of the reports of techniques used in a collection of fatal cases make one wonder that any other result was expected, quite apart from surgical interference. Many of these cases were everyday procedures which when ordinary methods are used carry a negligible risk.

Now interest has shifted to so-called hypothermia. Is it too much to hope that this new development will be investigated and tried out only in those few centres adequately equipped to deal with such a difficult investigation, and that the rest, until the results are clear, will continue to use the methods which have withstood the test of experience and have brought credit to the practice of anaesthetics? This will ensure that the ordinary run of anaesthesia is not reduced to an elaborate experiment in pharmacology, the results of which are at best problematical and impossible to assess.—I am, etc.,

Sutton, Surrey. JOHN H. WILLIS.

The Nephrotic Syndrome

SIR,—In your leading article on the nephrotic syndrome (*Journal*, December 26, 1953, p. 1419) you describe as contrary to expectation the relation observed by Professor John R. Squire (p. 1389) between the concentration of the plasma proteins and the osmotic pressure they exert.

More than 25 years ago I observed this relation and obtained a graph very like his. I used it to examine the changes which occur in nephrosis and arrived at somewhat similar conclusions. The results were published in 1926.[1] In the same year, E. B. Verney[2] also found this relation and, believing that the protein solution might resemble a highly compressed gas, proposed an equation to fit the graph for a limited range of values. The significance of Verney's equation and of several others which have since been proposed is still uncertain.—I am, etc.,

Belfast. E. B. C. MAYRS.

REFERENCES

1 *Quart. J. Med.*, 1926, **19**, 273.
2 *J. Physiol. (Lond.)*, 1926, **61**, 319.

Suxamethonium and Muscular Pain

SIR,—I was very glad to see that Dr. H. C. Churchill-Davidson has published (*Journal*, January 9, p. 74) his paper on "after-pain" following suxamethonium, and I can certainly endorse his findings. It is another good reason for extreme care in the use of relaxant techniques in out-patient departments.

In a report on suxamethonium for E.C.T., Dr. Rogers and myself[1] did not discover this condition. It is only during the past year that I have realized that pain could follow the use of suxamethonium in the *unconscious* patient, most commonly in out-patients but also in in-patients. After excluding the posture in a relaxed patient as a possible factor, I believe that suxamethonium has been the cause of neck and back pain and stiffness following tonsillectomy and laminectomy of sufficient severity to invite the diagnosis of poliomyelitis and meningitis respectively. This can indeed be a dangerous and disturbing result of anaesthesia.

Prevention has been attempted, after conversation with Drs. Churchill-Davidson and Chandler, with small doses of a curariform drug and also by the use of a dilute solution of suxamethonium without any spectacular success.

Lastly, I must say I have not Dr. Churchill-Davidson's complete confidence about administering neostigmine after any type of relaxant destroyed by pseudocholinesterase. Also, I feel he dismisses decamethonium too readily, for already a moderately effective antagonist, compound 49–204, has been described,[2] and I can partially confirm their findings in a small series of cases where this drug has been used, occasionally in association with edrophonium ("tensilon").—I am, etc.,

Twickenham. J. MIDDLETON PRICE.

REFERENCES

1 *British Medical Journal*, 1952, **1**, 1027.
2 Vandam, L. D., *et al.* (1953). *Curr. Res. Anesth.*, **32**, 113.

SIR,—In view of Dr. H. C. Churchill-Davidson's paper (*Journal*, January 9, p. 74), I wish to record my experience of suxamethonium administration.

Since May, 1953, I have given this drug 489 times to 62 patients for electro-convulsive therapy. During the last 250 or so administrations, I have been on the look-out for muscle pains, particularly subcostal, and have had only two complaints of pain of any kind. One obese female patient aged 46 complained on the day after treatment of "rheumatic" pains across both shoulders. She has had suxamethonium on eight occasions and has only complained once. The dose given to her was 35 mg. Another female patient aged 49 stated she had pains down the front of both legs on the day after she had been given 30 mg. of suxamethonium. She has been treated three times and has complained of pains only once. Each complaint occurred after the patient's first treatment. With regard to Dr. Churchill-Davidson's findings that exercise increased the incidence of the pains, I must point out that practically every one of these 62 patients was ambulant and was usually up out of bed within two hours of his or her treatment. At first it might be thought that these patients, some mentally defective, but most in severe depressive states, would be poor witnesses. However, I am assured by the medical and nursing staff that all these patients report every pain or ache, however trivial, and would not hesitate to complain of the type of discomfort suffered by Dr. Churchill-Davidson's patients.

There is a marked difference in the dosage given to my patients and to the patients in the published article. In

the first group the average dose was 88 mg. and in the second group it was 96 mg. Very few of my patients have had more than 50 mg.; most have had 30 to 40 mg. This may account for the higher incidence of muscle pains encountered by Dr. Churchill-Davidson.—I am, etc.,

Glasgow, S.2. A. KILPATRICK.

Malaria Prophylaxis

SIR,—In "Any Questions" under the heading of "Malaria Prophylaxis" (*Journal*, January 9, p. 107) it is advised that daily proguanil ("paludrine") prophylaxis should begin a fortnight before entering a malarious area. Why a fortnight? There appears to be no pharmacological basis for this procedure, and one of the advantages of proguanil as a prophylactic drug is that a loading dose is unnecessary. Provided 100 mg. is being taken every day, I know of no advantage in administering it before the individual enters a malarial area, other than establishing the habit of the daily dose. The question is one of considerable practical importance. In air travel in malarious countries, for example, it is not feasible to give proguanil to travellers and air crews for a fortnight before each journey.

Evidence that proguanil prophylaxis need not be commenced before exposure to infective biting was first obtained by Fairley *et al.*[1] Seventeen out of 17 non-immune volunteers receiving one single dose of either 50 mg. or 100 mg. of proguanil between 39 and 120 hours after exposure to mosquitoes harbouring a New Guinea strain of *P. falciparum* failed to develop malaria, though the controls did. Nine out of 10 volunteers receiving a single dose of 25 mg. of proguanil between 48 and 131 hours after exposure were likewise protected, and 6 out of 8 volunteers receiving a single dose of only 10 mg. of proguanil between 48 and 120 hours after exposure to infective biting were completely protected. On the other hand, a single dose of 100 mg. of proguanil failed to protect 24 hours and 144 hours or later after exposure to infective biting. Two out of 3 volunteers receiving a single dose of 300 mg. of proguanil at 168 and 192 hours respectively after exposure to infective biting developed overt malaria; the third who received 0.3 g. at 144 hours was protected.

Subinoculation experiments[2] in non-immune volunteers experimentally infected with *P. falciparum* while taking a daily dose of an antimalarial drug for the prevention or suppression of malaria revealed that with quinine, mepacrine, and chloroquine asexual parasites appeared in the blood of the recipient in sub-microscopic density on the 7th day (>144 hours) just as they did in the controls, whereas with proguanil asexual intracorpuscular parasites were never demonstrable in the recipients who invariably failed to develop malaria.

The Cairns experiments indicated that in falciparum malaria (New Guinea strain) (1) proguanil in one single dose of 50 to 100 mg. prevented malaria if given between the 39th and 131st hours following exposure to infective biting, (2) pre-erythrocytic parasites were much more susceptible to proguanil than were the corresponding asexual blood parasites, (3) when daily proguanil was being given to prevent malaria asexual trophozoites never reached the circulating blood.

As far as is known, these results hold for typical strains of *P. falciparum* everywhere. Even with the atypical West African strain studied by Covell *et al.*[3] where proguanil failed to clear the blood of falciparum parasites during overt malaria, no difference was demonstrated in its action as a causal prophylactic. Thus 10 out of 10 individuals receiving proguanil in a dosage of 50 or 100 mg. daily were completely protected against multiple infective biting.

In vivax malaria evidence obtained by subinoculation experiments[2] showed that (1) vivax parasites appear in the blood on the 9th day (>192 hours) after infective biting in volunteers taking quinine, mepacrine, or chloroquine just as they do in controls taking no drug, but with proguanil they never do so, and (2) proguanil inhibits schizogony of the pre-erythrocytic cycle, delays the appearance of asexual parasites in the blood, and prolongs indefinitely the incubation period while the drug is being taken. The fact that vivax relapses occur after proguanil administration is not due to failure of the drug to eradicate parasitaemia in typical strains of *P. vivax* but to the persistence of late exoerythrocytic parasites in the liver which from time to time erupt asexual trophozoites into the blood stream.

In the B.O.A.C. it has been the practice for the past 8 years to give 100 mg. of proguanil from the day of departure until the 10th day after leaving a malarious area. Sir Harold Whittingham, Director of Medical Services, B.O.A.C., informs me that during this period there have been only one or two malaria infections a year among a B.O.A.C. air crew strength of 1,360, about 1,000 of whom were constantly at risk. During this period the malaria rate has not exceeded 0.2% per annum, and careful inquiry has shown that every member of the air crew developing malaria had failed to take proguanil regularly.

No antimalarial drug has been studied more completely in man than proguanil. It would be unfortunate if a dosage regimen for malaria prevention and suppression so clearly indicated by extensive experimental studies under controlled conditions were not followed.—I am, etc.,

London, W.1. N. HAMILTON FAIRLEY.

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1 *Trans. roy Soc. trop. Med. Hyg.*, 1946, **40**, 133.
2 Fairley, N. H., *et al.* (1946). Ibid., **40**, 670.
3 Ibid., 1949, **42**, 343.

SIR,—Dr. Mary G. Phillips's experience with the ineffectiveness of pyrimethamine ("daraprim") as a prophylactic against *P. falciparum* is interesting (*Journal*, January 16, p. 155).

There can by now be little doubt that proguanil ("paludrine") taken daily, and the dose never missed, is by far the most effective drug in the prophylaxis against malignant tertian malaria; proguanil is, of course, a true causal prophylactic against the *P. falciparum* parasite. One wonders whether the dose of pyrimethamine, or alternatively the frequency of its administration, might be increased before it is condemned as being useless as a prophylactic against malignant tertian malaria.—I am, etc.,

Isleworth, Middlesex. JOHN C. L. ADAMS.

"Status Lymphaticus"

SIR,—Dr. H. B. Dodwell must be congratulated for tracing so satisfactorily to its ultimate source the "myth of status lymphaticus" (*Journal*, January 16, p. 149). The concept is fed to every student of medicine; it is mentioned in most textbooks of surgery and pathology, and most anaesthetic textbooks devote a section to the matter. It will be a difficult task to abolish the notion that status lymphaticus does exist, especially as it offers a plausible excuse for some "anaesthetic" deaths.

Some such deaths occurring in the first few minutes of anaesthesia could without doubt be traced to some lapse on the part of the anaesthetist, but may be ascribed to the "myth" on official records. This does not necessarily reflect upon the integrity of the anaesthetist, who may sincerely believe at the time that nothing untoward had occurred during the administration up to the moment of death; however, later investigation by an independent observer would, I am sure, bring to light little incidents which could in retrospect be interpreted as danger signals—the little cough, breathholding, tinge of cyanosis, pulse irregularities, etc.—and which could have been corrected by appropriate action in time to obviate the crisis.

Most cases of death allegedly due to status lymphaticus fall naturally into the age group 0–20 years, where the thymus is probably still in evidence and has not atrophied to the extent of making the diagnosis untenable or even ridiculous. The majority of cases of which I have heard occur in babies or young children undergoing a surgical operation of a comparatively trivial nature—for example, circumcision, herniotomy, excision of small skin tumours, tonsillectomy, incision of abscesses, etc.; occasionally

it occurs in the young adult and may be associated with circumcision or dilatation of the cervix. In such cases, where death unfortunately occurs, the child is reckoned to be a pretty normal specimen of humanity—it is only in retrospect that the possibility of status lymphaticus is considered and details are accumulated to prove it. The thymus gland exposed at necropsy is magnified to a suitable size in the imagination and the diagnosis is clinched. Everyone is satisfied that death was, perhaps, inevitable.

The commonly quoted fatal combination is that of a struggling, screaming child saturated with circulating adrenaline and a pad soaked in chloroform pressed firmly to his face, the child in the meanwhile being held down by a body of nurses and porters; the child suddenly goes limp, and this is assumed by all to be due to the action of chloroform—it is (with apologies to the addicts). Thus one more unfortunate is added to the growing list of victims of status lymphaticus. This state of affairs does not of course obtain in a well-run children's hospital, the children being asleep, in a "couldn't care less" frame of mind, or fully awake and prepared to co-operate, this latter state being achieved mainly by the manner and carefully chosen words of intelligent ward staff and to a lesser extent by the manner of the sympathetic, proficient, expert anaesthetist.

Similar deaths occur also with other anaesthetic agents in common use. Ethyl chloride is a well-known potent killer in inexpert hands. Soluble thiopentone certainly used to be a great lethal agent—due to actual or relative overdosage—and probably still is. Many deaths associated with its use in anaesthesia can be attributed to the rapid vasodilatation, greatly reduced venous return, lowered arterial pressure, coronary insufficiency, and ultimately death, which can and often does occur very quickly especially in toxic, dehydrated patients. Such cases can be labelled by thoughtless anaesthetists as idiosyncrasy, vagal inhibition, or status lymphaticus Again, other deaths occur following "safe" agents—for example, gas-oxygen-ether sequence—where the rapid manipulation of patients for surgery occurs in association with the too rapid onset of surgery.

One could multiply and elaborate these instances, but enough has been said to illustrate the idea that bad anaesthetic technique can be a potent source of these mysterious cases of status lymphaticus.—I am, etc.,

Aberdeen. DAVID A. FORBES.

SIR,—As Dr. H. B. Dodwell's article on "'Status Lymphaticus,' the Growth of a Myth" (*Journal*, January 16, p. 149) is largely a criticism of the views expressed by me in the seventh edition of *Recent Advances in Anaesthesia*[1] I may perhaps be permitted to reply. I cannot possibly cover the many points raised in the article by a letter and will confine myself to two only. Dr. Dodwell states in two places that W. N. Kemp, while believing in the existence of the condition, does not cite any actual cases. In Dr. Kemp's book *Elementary Anaesthesia*[2] chapter 23 is devoted to an excellent account of status lymphaticus and includes detailed reports of seven patients with references to forty others, most of which were not associated with anaesthesia.

Dr. Dodwell also states that he cannot find any account of the late Sir Bernard Spilsbury's views on the subject. Sir Bernard kindly discussed the condition with me fully at a time when I was about to consign it in my own mind to the category of discarded fables. Although he disliked the term status lymphaticus, Sir Bernard was convinced of the existence of a condition in children and young people who were more likely to die from sudden cardiac failure than normal individuals and in whom certain definite pathological changes could be demonstrated post-mortem. The chief findings were an enlarged thymus, general lymphatic hyperplasia, a narrowed aorta, and fatty infiltration of the heart muscle. I was later fortunate enough to see Sir Bernard demonstrating two classical examples of the condition in children who had died suddenly for no obvious reason and with no other post-mortem abnormalities than those mentioned above. Sir Bernard Spilsbury told me after his retirement he proposed to go through his post-mortem notes on cases of status lymphaticus (between 100 and 200) and to write a paper based upon them. Unfortunately, his tragic death prevented this project from being accomplished, but I would think that, if anyone had the time and ability to peruse and classify the immense number of meticulously accurate case reports which he left, not only would status lymphaticus be clarified but also other obscure pathological conditions. Nobody who saw Sir Bernard's superb technique in the post-mortem room or who had listened to his logical reasoning in the lecture theatre or in the law courts could possibly imagine him capable of slipshod work or muddled thinking, and it is incredible that he should have pursued a chimera for so many years.

For this and other reasons I personally changed my view, and, while freely admitting that status lymphaticus has often been used quite unjustifiably as an escape mechanism by anaesthetists and others, I now believe that the condition does exist.—I am, etc.,

London, E.C.1. C. LANGTON HEWER.

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2 *Elementary Anaesthesia*, 1948. Baillière, Tindall and Cox, London.

Radiology and Lumbar Disks

SIR,—In his letter (*Journal*, January 23, p. 213) Mr. J. R. Armstrong has left out an important step in the treatment of disk lesions. The immediate treatment of most cases is not mere rest and immobilization, it is *reduction* followed by resting the joint in a good position by various forms of immobilization. Were this principle, so often applicable to fracture with displacement, applied equally to displacement of part of a disk, much of the prolonged disablement that Sir Max Page rightly deplores would be avoided. Moreover, the reproach to our profession represented by osteopaths' successes would cease as well.

When a displacement is present, reduction followed by its maintenance compares favourably, in theory and in practice, with immobilization alone.—I am, etc.,

London, W.1. JAMES CYRIAX.

SIR,—Your leading article (*Journal*, December 19, 1953, p. 1363), entitled "Radiology and Lumbar Disks," interested me greatly, as it was inclined to bear out my own personal opinion, that radiology is useless in the diagnosis of disk protrusions, but should be used to rule out any differential diagnosis.

The great number of disk lesions presenting themselves to the doctors nowadays surely rules out myelography as a diagnostic procedure. Thorough clinical examination should give the proper diagnosis without any radiological aid, except in a few cases.

I ought to agree with all that Sir Max Page says in his letter on this subject (*Journal*, January 9, p. 97), as I had the great fortune to be one of his dressers as a student, but I cannot agree with him that any diagnosis can be premature if correct. The sooner a disk protrusion is diagnosed the easier the treatment and the earlier the recovery. I do, on the other hand, agree with his complaint of the time wasted when the patient has to wait to see a specialist and have an *x*-ray. As I explained in my article "Manipulation and Accurate Manual Methods in General Practice" (*Journal*, July 4, 1953, p. 18), general practitioners should be trained in this work, both to save time and to prevent complications.

I also agree with him that prolonged partial immobilization is a too frequent routine, as manipulation or spinal traction will quickly relieve the majority of cases.—I am, etc.,

Hoddesdon, Herts. R. BARBOR.

A Cosmetic Amputation

SIR,—Contrary to reactions of almost unqualified disapproval which Mr. Ian Lawson Dick's letter (*Journal*, January 2, p. 45) aroused in Professor Bryan McFarland (*Journal*, January 16, p. 159), Mr. Dick's strongly expressed and important observations concerning the cosmetic amputation brought me great satisfaction.

May I record that 28 years ago, when I was a surgical registrar, following accidental infection in the operating

theatre eventuating in chronic periosteomyelitis, it became necessary for me to have my left index finger amputated. Desiring an oblique section of the distal third of the shaft of the metacarpal bone, and anxious to have weighty approbation for this then seldom-performed operation, I consulted the late Professor Schoemaker, of The Hague, Professor Ernest Groves, of Bristol, Sir Robert Jones, of Liverpool, Professor de Quervain, of Geneva, as well as Sir Hugh Rigby, Mr. James Sherren, and Sir Robert (then Mr.) Milne, of the London Hospital. Independently, with the single exception of Professor de Quervain, this illustrious assembly were adamant : " Retain the head of your metacarpal bone —a surgeon requires manual strength as well as skill " was the refrain. Notwithstanding, I persuaded Sir Hugh Rigby to carry out the operation of my choice. Had the then orthodox operation been performed, for several reasons it is unlikely that I would have been able to follow my calling *in toto*.

Since then I have performed this cosmetic amputation several hundreds of times, always to the patient's eventual satisfaction. The cosmetic operation is suited eminently to women (without exception), those who follow the learned professions, business men, clerks, and the majority of highly skilled workmen. In my considered opinion it is the greater amount of compensation awarded to the plaintiff at law for the sacrifice of the head of a metacarpal that has unavoidably biased current practice.—I am, etc.,

London, W.1. HAMILTON BAILEY.

Sickle-cell Anaemia

SIR,—With reference to Dr. H. Lehmann's letter on sickle-cell anaemia (*Journal*, November 28, 1953, p. 1217) and to the possible explanation as to the survival of the sickle-cell trait—including the evidence produced by Brain[1] that the sickler may have an advantage over the non-sickler in respect of some protection against red-cell parasitization by the malaria parasite—we are able to support this latter hypothesis, our evidence having been published in the Tanganyika Annual Report of the Medical Laboratory for 1952, in which it is stated:

" One of the unexplained facts about the congenital sickling abnormality is its apparent survival value in spite of the fact that the rapid homozygous sickler is liable to die in the early years of life of sickle-cell anaemia. It appeared that this survival value may lie in there being some advantage to the heterozygous sickle-cell trait individual in respect of decreased susceptibility of a proportion of his red cells to parasitization by *P. falciparum*. To test this theory watch was made for a heavy *P. falciparum* parasitization in a sickle-cell trait individual. This was eventually found. This patient's blood was then sickled by the simple wet sealed preparation technique, after which the cover slip was removed, the cells fixed by rapid drying and stained by Leishmann. The stained film showed large numbers of parasitized cells, but it was very obvious that these were well formed and not sickled. On the other hand, very few of the sickled cells were parasitized, although the majority of the cells were in fact sickled. The explanation of this phenomenon needs careful investigation; there is the possibility, however, that the sickle-cell haemoglobin may be an unsuitable intracellular environment for the growth and metabolism of the trophozoite. Alternatively, parasitization of a cell containing a certain proportion of a sickle-cell haemoglobin may lead to its *in vivo* sickling and phagocytosis, thus terminating the reproduction cycle in the case of cells so invaded."

It should be noted that, although the sickle-cell trait incidence in Dar es Salaam is 20%, only one of 16 heavy malaria infections was in fact sickle-cell trait positive. It is also relevant to record that in a sickle-cell survey carried out by Mackey[2] in Dar es Salaam 16% of 330 infants, average age 6 months, were sickle-cell trait positive as opposed to 23% of 283 adults, average age 26 years. Dar es Salaam is in a hyperendemic malarious area, and it would seem that in this area the sickler has a better chance of survival to adult life than the non-sickler.—We are, etc.,

J. P. MACKEY.
F. VIVARELLI.

Dar es Salaam.

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Ophthalmic Surgery in India

SIR,—Dr. J. N. Tennent's article (*Journal*, January 2, p. 39) does far from justice to Rai Bahadur Dr. Mathra Das, the founder of blind relief camps. As the Rai Bahadur put it to me, he had early realized that the Rolls-Royce methods employed in hospitals were not capable of touching the fringe of the problem of cataract in India. Something of the nature of modern mass production was required, and he found it in the blind relief camps. When I last saw him he had the intention of retiring when he reached his 200,000th extraction, but the many calls on his skill prevented it. His records showed a " casualty " rate of less than 1%.

In company with a member of our staff, who had completed six months as junior and six months as senior ophthalmic surgeon, I visited one of Dr. Mathra Das's camps, and watched his methods. The average patient, after walking from his village to the camp, presented himself in the early part of the day and, after he had his preliminary examination by the surgeon, was given a card the colour of which decided whether he was deemed fit to stay for operation or to be sent back home again. Selected patients were given a wash-out, the anaesthetic, and might be on the table within the half-hour. With the help of a well-trained assistant, Dr. Mathra Das removed four cataracts per minute. Bandaging, etc., was done by trained assistants, and by the time the surgeon had finished at table four a fresh patient was ready at table one. He did nearly 400 operations that day, and a week later I returned to the camp to ascertain the results. Three of them had gone " wrong," and one of the three was a woman who disliked the surgical dressing enough to replace it by the softer stuffing of her mattress. Even if she be included among the casualties, the rate was still less than 1%, a truly remarkable achievement. The rate for that particular camp correctly sampled Dr. Mathra Das's overall rate for 200,000.

In my travels round India I heard much criticism of Dr. Mathra Das's technique, so, from his lecture, did Dr. Tennent. If such criticisms were comprehensively based there should have been something like 300 casualties at the camp which I visited and inspected instead of 3. The missing factor, so I suggest, is the high degree of acquired immunity which the Indian ryot's cornea must acquire against septic organisms through its owner living amid so much dust. Dr. Mathra Das had his own private camp hospital just outside Lahore where he did an easy hundred operations weekly, and trained his assistants in after-care before he took them to any outside camp. A month in that camp would give even a compounder more experience of this after-care than many of our own young specialists have had. Some of the assistants left behind for after-care were of compounder status, but they were far from inexperienced at the after-care of cataract. The head assistant was of the sub-assistant surgeon grade with a four-year qualification period.

My own opinion of Dr. Mathra Das, given in my book, *Climate and Labour*, is that no other Indian has done so much good to other Indians as he has. After all, 200,000 cataracts make an easy record which none of our eye specialists can even approach, and, doubtfully, any of our hospitals.—I am, etc.,

Malta, G.C. W. BURRIDGE.

Eosinophils in the Sputum

SIR,—In connexion with the paper by Dr. John Vaughn (*Journal*, January 2, p. 27) I should like to mention the following case in which I was concerned, from the laboratory point of view, a couple of years ago, and which he may think supports his thesis that the presence of eosinophils in the sputum is a manifestation of a blood eosinophilia.

The patient was a man of 18 who presented with fever and migrating opacities in the lungs on radiography. The individual lesions were present for a few days and would then disappear, to be followed after a short interval by a

similar shadow in another part of the lung field, together with a brisk rise of temperature. I no longer have the records of the case, but as far as I remember the blood leucocytes numbered about 20,000 per c.mm., with up to 92% eosinophils. Between attacks the total count was about 5,000 per c.mm., with 40 to 50% eosinophils. There was also anaemia. At all times during the illness, and particularly during the acute pulmonary incidents, the sputum contained very large numbers of eosinophils. The most interesting point about the case is that the patient died a few weeks later in another hospital, where at necropsy the morbid anatomical findings were those of a classical myeloid leukaemia. I did not have an opportunity of seeing the sections myself. Such cases of eosinophilic leukaemia, though rare, are described in the literature. The important point, however, is that in this case a high blood eosinophilia, caused by a primary marrow dysplasia, was associated with what might be considered a Loeffler's syndrome and a marked excretion of eosinophils in the sputum.—I am, etc.,

Liverpool, 7. C. H. JONES.

Ulcerative Colitis

SIR,—I read with interest Sir Robert Hutchison's letter on ulcerative colitis (*Journal*, January 9, p. 98), and, whilst not wishing to venture into the aetiology of the condition, I should like to mention one point of interest.

When Case 4 in Mr. Stanley O. Aylett's series (*Journal*, December 19, 1953, p. 1348) was admitted to hospital there was for some time doubt about the diagnosis in view of her extreme youth (in actual fact she was aged 9 years when first admitted). In view of this, exhaustive tests were carried out and much questioning of the parents took place. Eventually it was discovered that the bowel symptoms were of acute onset dating from a most peculiar incident. She had met her parents returning from a Jewish funeral and had rushed in hysterics to a friend living in a flat in the same block, where she remained at her own request for several days. During that stay her bowel gave trouble for the first time. I am aware that this can be dismissed as coincidence, but at least it is peculiar coincidence.

In all fairness I would say, and I think Mr. Aylett would agree, that none of the other patients in the series could be classified as "emotionally immature."—I am, etc.,

Fowey. MARTIN LUTHER.

SIR,—With reference to Sir Robert Hutchison's plea for the return of appendicostomy and colonic lavage as "far the best treatment" for ulcerative colitis (*Journal*, January 9, p. 98), I hasten to suggest danger. The results of our research in the *x*-ray department at St. Mark's Hospital for Diseases of Rectum and Colon reveal that quite a large number of cases labelled "ulcerative" colitis by the clinician have been shown at *x*-ray examination, and later confirmed by colectomy, to have no ulcers at all. Some of the so-called "fibrous strictures" have been found to relax after the employment of antispasmodics, as recorded at subsequent *x*-ray examination. Those that have had colectomy performed show only hypertrophy of the muscle wall and no fibrous changes. Perhaps most alarming of all has been the finding by Dr. Dukes at St. Mark's of seven microscopic cancers lined up in a section of the colon in a case of ulcerative colitis. Then there is the devastating, rapidly advancing destructive "polypoid" type of colon, studded with numerous groups of polyps, essentially inflammatory in nature, which do not turn malignant, whereas the familial variety do of course. The picture in these cases can alter so rapidly, showing in the beginning an almost normal bowel, and then within the short space of six months present a shrunken colon literally studded with polypi, with practically complete destruction of the mucous membrane. The patient goes downhill rapidly. Such cases are easily demonstrated by opaque enema examinations and especially if reduction density technique is carried out. Then there is tuberculous colitis, the syphilitic colon, the dysenteric colon, and our old friend diverticulosis with diverticulitis which essentially starts as a localized colitis (sometimes preceded by a period of obstinate constipation) and so ending eventually as a state of diverticulosis, with possibly from time to time recurrent diverticulitis. Modern medicine to-day does not approve of such crude methods of treatment as appendicostomy to dissipate seven microscopic cancers, or some of these tragic cases of polypoid colitis.

I have great respect and admiration for Sir Robert's brilliant talents and his numerous contributions to medicine, and therefore, as a countryman of my own, same university, etc., I make the following suggestion with great respect. Might it just possibly be that some of these cases Sir Robert treated with appendicostomy and lavage with such success were cases the clinicians labelled in those days as ulcerative colitis, but in the light of modern advances they were probably only cases of chronic colitis, admittedly of long duration, but not ulcerative? Indeed, until recently some of the so-called "ulcerative" colitis cases were only labelled "ulcerative" for no better reason than that the course of the illness had been long and uninterrupted over a period of years. I have cases on record at St. Mark's of 5, 10, 20, and 27 years' standing labelled as "ulcerative" colitis, which at *x*-ray examination present a colon with circular and longitudinal muscle tone not far from normal and no signs of fatigue at all, and certainly no ulcers. In other words the clinical classification of "acute," "subacute," and the "chronic" is quite out of date, and in the *Lancet* (January 16, 1954, p. 159) I have briefly described our new *x*-ray classification of colitis which has now been in operation at St. Mark's for some time back.

No, as I see it, ileostomy is only performed essentially as a preliminary, prior to colectomy, and only resorted to in these true cases of ulcerative colitis where medical treatment has failed and appendicostomy or any other form of treatment has proved useless in what really amounts to a disease which is a potential precancerous disease of the colon.—I am, etc.,

London, W.1. NORMAN P. HENDERSON.

Antibiotics in Bacteriaemia

SIR,—In the discussion on antibiotics in bacteriaemia (*Journal*, December 19, 1953, p. 1376) Dr. M. Anthony Peyman states that "it is perfectly possible for a patient to be cured of a bacterial infection by an antibiotic while *in vitro* tests demonstrate the organism to be insensitive to that antibiotic." This rash statement is partly upheld by Dr. A. Lawrence (*Journal*, January 9, p. 100). I know of no satisfactory evidence whatever to support it.

The difference of opinion may be due to lack of definition of "*in vitro* resistance." Unfortunately there is no standard method for sensitivity tests and therefore reports vary from different laboratories. The popular and rapid paper disk method is a good indicator of sensitivity when inhibition zones are large, but it is not always appreciated that small zones, or even absence of inhibition, may not indicate an untreatable degree of resistance. If a weak solution of antibiotic is used to prepare the disks (for fear of overestimating sensitivity) and if the potency of each disk is not controlled on each plate culture, resistance is likely to be falsely reported from time to time. I would not consider a microbe isolated from the blood to be resistant *in vitro* until titration in a serum medium, in parallel with a control strain of known sensitivity, had shown its growth to be unaffected by a concentration of antibiotic higher than that obtainable in the patient's serum.

Cure of a patient suffering from bacteriaemia by a drug which has been reported inactive in the laboratory must not lightly be taken as evidence that conditions in the blood stream favour antibiotic action. It is an indication for further tests on "resistant" microbes, not for submitting patients to large doses of toxic drugs regardless of the laboratory report.—I am, etc.,

London, W.C.1. E. JOAN STOKES.

Studies of a General Practice

SIR,—The survey of work in general practice in an urban area undertaken and reported upon by Dr. E. M. Backett and others (*Journal*, January 16, p. 109) is of the greatest interest, and it may be opportune to report, and compare where possible, a survey taken over a period of one year (November, 1952, to October, 1953) in an N.H.S. practice classified as rural. This survey was concerned only with diseases and the amount of work involved.

The practice consists of a partnership of two, each partner, as far as possible, seeing his own patients. The survey was taken of one of the partners' work, the N.H.S. list varying over the year between 2,100 and 2,200 persons. The practice area is in a radius of 10 miles from the surgery with a handful of patients up to 12 miles. The hospital and maternity home are 11 miles away.

The N.H.S medical work was 9,675 items, consisting of 5,017 visits (51.8%) and 4,658 consultations at the surgery (48.2%). Work such as the signing of pension forms, certificates for coal and housing, life assurance reports and examinations, telephone conversations to hospitals, etc., was not included in the 9,675 items listed, nor were long conversations with patients (if they did not directly concern that person's disease—if any). For the purpose of the survey, diseases were classified under 17 headings as shown on the chart. The small number of patients referred for specialist opinion is mainly due to the fact that the hospital laboratory and *x*-ray department are willing to carry out any investigation on our direct request. This facility is very much appreciated.

	No. of Consultations Plus Visits	Consultations Plus Visits % (Approx.)	No. of Cases Seen (New)	New Cases % (Approx.)	Referred to Specialist
1 Respiratory ..	1,952	20	578	20	33
2 C.V.S.	1,315	14·5	144	5	8
3 Digestive system ..	640	6·75	229	8	12
4 Blood diseases ..	433	4·5	62	2	2
5 Orthopaedic ..	790	8	285	10	27
6 Endocrine disturbances	155	1·5	41	1·5	1
7 Midwifery ..	483	5	54	2	4
8 E.N.T.	751	7·75	443	15·5	24
9 Neurosis	424	4·5	94	3·25	9
10 Skin diseases ..	555	5·75	266	9·25	12
11 Infectious diseases	350	3·5	105	3·5	1
12 Minor surgery ..	327	3·25	117	4	2
13 Accidents ..	325	3·25	167	6	8
14 Renal system ..	287	2·75	60	2	6
15 Gynaecology ..	225	2·25	50	2	14
16 Eyes	174	1·75	118	4	8
17 Surgical	489	5	62	2	25
Total ..	9,675	100	2,875	100	196

Comparing Dr. Backett's figures in the urban practice with the above rural practice, it can be seen that there is no great variation—that is, (1) psychiatric disorders, or neurosis, involved 5% of all cases in the urban area and 3.25% in the rural, while work involved was 1 to 7% urban and 4.5% rural; (2) cardiovascular system: 3% of all cases urban and 5% rural, work involved 2 to 10% urban and 14.5% rural; (3) skin: 11% of all cases urban, 9.25% rural, work involved 6 to 12% urban, 9.25% rural. The one outstanding variation between the two practices is in the percentages of work involving visits to the patient's home—36% urban, 51.8% rural. There are a few patients who think that it is easier for the doctor to travel to his house than for him or her to get to the surgery. There is also the "snob" element in a few patients which is difficult, and not always wise, to break. It may be that the rural patient has to be iller than his urban brother before he seeks advice (although up till now this had never occurred to me). Or perhaps it just goes to show that no two practices are alike. If the latter is the case, is it really worth wallowing in a mass of figures?—I am, etc.,

Brightlingsea, Essex. JOHN MIDDLETON.

Training General Practitioners in Psychotherapy

SIR,—Dr. Michael Balint's warm-hearted and sympathetic article on "Training General Practitioners in Psychotherapy" (*Journal*, January 16, p. 115) must have been read with gratitude by many analytical psychotherapists. The practitioner's relationship to the psychiatric consultant of the analytical persuasion is one of the most complex and paradoxical issues in present-day medicine. The author describes certain aspects of this relationship which exist on both sides. From the long waiting-lists in all psychiatric institutions and the longer ones in the few existing analytical clinics, it becomes quite obvious how much in need the practitioner feels of the help of medical psychotherapists. Yet when he sends his patient to the analyst, he is often—certainly more often than not—ignorant of the analytical methods and its many implications. He so often feels that analysis is glorified pep-talking, only more expensive, and that if he had the time he could do most of it himself. He usually has heard little of positive and negative transference and less of the meaning of symbols in dreams and free associations. He may marvel at the long time an analysis with one of his patients may take and at the continuation of symptoms even after many months of treatment. He may even wonder whether the relationship between patient and analyst, which is based on the transference, is the right thing for his patient.

All this may make the practitioner into a far from wholehearted ally of the very specialist whom he has called in. As soon as the practitioner's co-operation with the psychotherapist becomes less than whole-hearted, the analysis may be adversely affected, and the patient may then, with the intuitiveness of the neurotic, begin to see a way of "escape from cure" by playing off the two authorities one against the other. I am quite sure that the practitioner has sometimes most unsympathetic colleagues among the analytical specialists and finds that the latter may have little idea of his own work and its complexity. Ideally, therefore, not only should the practitioner learn much more about analytical psychotherapy in practice, but equally the analyst should miss no opportunity to acquaint himself with the work confronting the practitioner in his daily tasks. Dr. Balint's article may inspire many of his readers to seek a closer understanding and more intimate knowledge. Perhaps it will become possible, not only in London, to have training and discussion groups established, which would be such a blessing to both practitioner and specialist and bring more effective help to so many neurotic patients.—I am, etc.,

Edinburgh, 9. W. P. KRAEMER.

SIR,—In his good and stimulating paper, "Training General Practitioners in Psychotherapy" (*Journal*, January 16, p. 115), Dr. Michael Balint says that "the only training which systematically caters for these difficulties [difficulties in personality of the prospective psychotherapist] is the psycho-analytic training."

May I be allowed the hospitality of your columns to correct and supplement this statement? The Society of Analytical Psychology also provides a training with identical aims.—I am, etc.,

London, W.1. MICHAEL FORDHAM.

Treatment of Angina

SIR,—Dr. David Weitzman's paper (*Journal*, December 26, 1953, p. 1409) on penta-erythritol tetranitrate (P.E.T.N.) raises a number of interesting points, and his somewhat inconclusive results correspond to those which other observers have found with this preparation and with its precursor, erythrol tetranitrate (E.T.). Twenty years ago Evans and Hoyle[1] reached the conclusion that E.T., in common with a large number of other potential vasodilators, had practically no value in the management of angina pectoris, but their conclusion is not borne out by practical experience spread over a large number of cases.

The unpredictable effect of P.E.T.N. and E.T. is common to both preparations, but the former has fewer side-effects and has been better tolerated in my own series.

The error into which we seem to have fallen is that of regarding all cases of angina pectoris as having identical aetiology, although everyone is familiar with the mild sclerosis which can be found at necropsy in a patient who has had severe angina and, at the other end of the scale, the gross calcification of the main coronary arteries in patients who have never suffered from ischaemic pain. It is hardly surprising that some patients do not respond to these long-acting vasodilators whose potency is relatively low, even though they respond so well to glyceryl trinitrate. In view of the findings in my own series, which are comparable with those reported by Dr. Weitzman, I am now concentrating on treating those patients who derive benefit from P.E.T.N., and I am trying to assess its value by the use of genuine and identical dummy tablets.

This seems to be an example of a condition where a direct statistical approach may give a fallacious answer, and to work on an unselected series may bring into disfavour a drug which seems to me to have a definite place in the management at least of some patients with angina pectoris. —I am, etc.,

London, W.1. A. L. WINGFIELD.

REFERENCE

[1] *Quart. J. Med.*, 1934, **27**, 105.

POINTS FROM LETTERS

Disease and the Pig Bin

Dr. KATHLEEN VAUGHAN (London) writes: I have not seen any report on the remarkable disappearance of the ordinary house-fly with a soft proboscis and its replacement by a fly looking much the same but furnished with a spike with which he draws your blood. Squash one of these and there is always red blood inside. Where do they breed? In those awful tins labelled "Pig's Food," where bits of meat, stale vegetables, tea leaves, carpet, and paper bags are deposited and left without early removal or disinfection. No self-respecting pig would eat the contents. May not the stinking pig's food bin prove to be the breeding ground of diseases whose origin is still obscure?

Masked Appendicitis

Dr. R. G. WIGODER (London, S.E.6) writes: A male patient, aged 50, walked into my surgery complaining of upper abdominal pain, which he said had been present for about 24 hours. He had no nausea or vomiting and felt well except for this pain. His temperature and pulse were normal, tongue clean, lungs normal, and the only abnormal physical sign found was, to my mind, slight rigidity and guarding in the right iliac fossa. There was no tenderness in the right iliac fossa, but there was rebound tenderness present. He was sent immediately to hospital—query appendicitis—and on examination they found only some voluntary guarding in the right iliac fossa, but no rigidity. A laparotomy was performed and an acutely inflamed appendix was removed. The patient made a satisfactory recovery following operation. This case serves as a reminder that an acute appendix can be present with only minimal symptoms and signs.

Sale of Antibiotic Lozenges

Dr. G. FIELDING (Nottingham) writes: It appears that "tyrozets" and similar antibiotic throat lozenges can be freely bought in any chemist's shop over the counter. I saw a patient to-day with a typically inflamed denuded "antibiotic" tongue who had treated herself with a tube of these lozenges. As these tablets are potentially dangerous and also contain 5 mg. of benzocaine, their sale should be restricted in the same way as penicillin lozenges already are.

Disposal of Anaesthetics

Dr. L. RENDELL-BAKER (Cardiff) writes: In his letter Dr. M. Essex-Lopresti (*Journal*, December 26, 1953, p. 1433) complains that its blue colour prevents the use of waste trichlorethylene ("trilene") for cleaning purposes. He will find that a small bag containing activated charcoal (as used in laboratories for gas absorption) will remove the waxolene-blue dye from the trichlorethylene, leaving a clear fluid which is quite suitable for cleaning and degreasing purposes. The waste trichlorethylene and ether can then both be of use.

Obituary

Lord GEDDES, P.C., G.C.M.G., K.C.B., M.D.

Dr. J. B. WRATHALL ROWE writes: Your obituary notice (January 16, p. 160) of Lord Geddes makes no mention of the fact that, in addition to his other talents, he was an accomplished musician. During the first few years of the century he composed a number of airs for marching songs and wrote choruses for smoking concerts. One of the best known of these songs is "Route Marchin'," with words by Rudyard Kipling, published in the *British Students' Song Book*. It is probable that other compositions of his would have become well known had it not been for the fact that his musical MSS. were stolen from his tent when he was in camp at the Curragh before the 1914–18 war.

Dr. D. SAGE SUTHERLAND, formerly medical superintendent of Monsall Isolation Hospital, Manchester, died suddenly at Edinburgh, where he was living in retirement, on January 9 at the age of 78. Donald Sage Sutherland was born at Lochaber, Inverness-shire, on March 19, 1875, the son of the late Rev. Donald Sutherland, and was educated at Garnethill School and Glasgow University, where he graduated M.B., Ch.B. in 1898. He received a commendation for his M.D. thesis in 1903. After a brief period in general practice at Keighley, Yorkshire, he held the post of senior resident house-physician and surgeon at the Cumberland Infirmary, Carlisle, his work there being interrupted by a period of service as a medical officer in the South African Field Force in 1900–1. From Carlisle he moved to London to begin his long association with the fever hospital service. After holding the appointment of assistant medical officer at Brook Fever Hospital, Woolwich, under the old Metropolitan Asylums Board, he became medical officer at the South-Western Fever Hospital, Stockwell, in 1906 and remained there until 1914. An enthusiastic Territorial—he joined the force in 1909, when he was attached to a London brigade of artillery—he was transferred to the 2/1 City of London Field Ambulance as second in command when war broke out in 1914. He served throughout the war, and in 1917 became commanding officer of an isolation hospital at Calais.

On his return to civilian life Dr. Sage Sutherland became senior medical officer at the Eastern Fever Hospital, Homerton, in 1918 and held the post until 1923, when he was appointed medical superintendent of Monsall Isolation Hospital, Newton Heath, Manchester. He also became clinical lecturer in infectious diseases in Manchester University. In Lancashire he continued his connexion with the Territorial Army, first with the Manchester Artillery as medical officer and then, in 1930, when he was promoted to the rank of lieutenant-colonel, as officer commanding the 2nd Western General Hospital. He was awarded the Territorial Decoration in 1925 and he retired from the Territorial Army in 1934. When war broke out again in 1939 he was engaged for a short time as officer in command of administration at the Territorial depot of the R.A.M.C. in Manchester. On his retirement from the post at Monsall Hospital in 1941, Dr. Sage Sutherland went to live first at Ambleside and later at Edinburgh. He leaves a widow and two young sons.

Dr. J. W. DEW, who was in practice at Horsham in Sussex for many years, died at his home on December 15, 1953, at the age of 66. John Westcott Dew was born at Hoddesdon, Hertfordshire, on January 10, 1887, and was educated at Tonbridge School, where he was head boy and for two years captain of football and cricket. His career at Cambridge, where he was at Clare College, was equally distinguished,

and he took a first in Part I of the Natural Sciences Tripos and went on to the London Hospital with an exhibition. He graduated M.B., B.Chir. in 1912, and held the appointments of house-surgeon and ophthalmic house-surgeon at the London Hospital. He served throughout the war of 1914–18 with No. 10 Casualty Clearing Station, becoming a surgical specialist with the rank of major. He was twice mentioned in dispatches and in 1918 was awarded the Military Cross for attending wounded under heavy fire. After the war he settled at Horsham in 1919 and soon acquired a busy private practice. He also joined the staff of Horsham Hospital and became responsible for a large share of the operative work there. Dr. Dew was in fact that rare combination, a first-class general practitioner and a very good surgeon: not only was he a skilled operator but he possessed that invaluable asset, sound surgical sense. His opinion on a difficult abdomen was eagerly sought and willingly given, and he rarely made a mistake. But he will be remembered chiefly as a most lovable individual. By nature he was modest and unassuming and his innate honesty and sincerity made him beloved by his patients, to whom he was counsellor and friend. Many of his poorer patients could tell stories of his kindness quite outside the accepted obligations of a doctor. His tact and common sense were a great asset to the various hospital committees on which he served for many years. He was honorary secretary of the Horsham Division of the British Medical Association from 1922 to 1925, and he had a wide range of interests outside his profession. He was a first-class shot and a keen sportsman, and excelled at all games. Not only did he play them very well but he had a gift of inspiring others with his enthusiasm and obvious enjoyment. He was a keen philatelist and a talented musician, being a faithful member of the church choir. But probably his greatest love was bird-watching and bird-photography. Some of his happiest memories were of holidays spent, together with his wife, following this hobby, in some distant corner of Scotland or on some small island off the coast. His photography was of a very high order, evidence of many hours of patient watching and waiting. He worked hard and played hard, and never spared himself. He worked to the end, knowing well that the cardiovascular disease from which he was suffering might at any time prove fatal. Our sincere sympathy goes out to his widow, and to his two sons, the elder, Dr. J. A. Dew, having recently joined him in practice at Horsham.—G. S. M.

Dr. W. H. ROWELL, who was in general practice for 14 years before he joined the public health service, died suddenly in hospital on January 4 at the age of 79. Born on May 8, 1874, William Henry Rowell studied medicine at Newcastle-upon-Tyne and graduated M.B., B.S. from the University of Durham in 1895. He proceeded to the M.D. three years later, and obtained the degree of B.Hy., with honours, in 1899. Serving as a volunteer in the South African war, he took part in actions at Kimberley and in the relief of Mafeking in 1900. On his return home he was elected an honorary freeman of the city of Newcastle-upon-Tyne. After taking the D.P.H. in 1901, he settled at Grimsby, where he spent the first part of his professional career in general practice until the outbreak of war in 1914. Already a Territorial attached to the Lincolnshire Yeomanry, he served throughout the first world war, attaining the rank of major and being twice mentioned in dispatches. In 1919 he was appointed O.B.E. He then returned to civilian life and in 1920 he took the degree of D.Hyg. before joining the staff of the public health department at Stockport, where he was one of the pioneers in the school health service. He worked as assistant school medical officer in that town until 1943, when he retired to Grange-over-Sands to be near the lakes he loved so well. The pleasant and soft surroundings of Grange, where he enjoyed his 10 years of leisure, were in keeping with his own nature, for he was a modest man, full of love and sympathy for his fellow men. His end came quickly, with a sudden heart attack, as he would have wished. He is survived by his wife.—J. Y.

Medical Notes in Parliament

Treatment of Blindness

Mrs. EIRENE WHITE asked the Minister of Health on January 21 if he had considered the report of Professor A. Sorsby on the causes of blindness, and what action he proposed.[1]

Mr. IAIN MACLEOD said he had asked hospital authorities to review urgently, and where necessary improve, their arrangements for the treatment of persons suffering from eye diseases, in particular cataract and glaucoma. He had also asked medical officers of health to include in their annual reports for 1953 information about the steps taken to follow up cases shown on registration as requiring remedial treatment. He was considering whether the examination at registration could be used to obtain better information on the possibilities of the blindness being relieved.

Mr. SOMERVILLE HASTINGS suggested that the Minister should consider sending to general practitioners a request that all cases of incipient blindness not due to errors of refraction might be sent at once to an eye specialist. Mr. MACLEOD said he would consider it.

Mr. BARNET JANNER asked the Minister of Health what response he had received from his circular to hospital boards asking them to review urgently their arrangements for the treatment of ophthalmological patients. Mr. MACLEOD replied that there had not yet been time for boards to decide what action should be taken, and in any case he had not thought it necessary to require boards to submit formal proposals on this.

Cancer Research

Mr. NORMAN DODDS, questioning Mr. Iain Macleod on January 21 about cancer research and treatment, said there was a feeling among the public, rightly or wrongly, that not all that might be done was being done. Mr. MACLEOD replied that it was important to keep the matter in perspective. Apart from cancer of the lung, of which there had been a considerable increase, the causes of which were still in medical and scientific dispute, and a small number of other sites, the death rate for cancer had not increased when allowance was made for the increase in the age structure of the population. The increase was not confined to this country, and they were doing everything they could to combat it.

Health Service Specialists

Mr. A. BLENKINSOP asked the Minister of Health on January 21 for information about the number of full-time and part-time specialists employed in the Health Service, and asked him also to keep this matter very much in mind, in view of the strong feeling that part-time specialists were being too much favoured, to the detriment of full-time specialists, and that this might have a dangerous effect on the Service. Mr. MACLEOD said that he would bear it in mind.

Mr. H. MARQUAND asked the Minister if he would care to deny the feeling in some parts of the medical profession that he might have been encouraging or directing a change from full-time to part-time service. Mr. MACLEOD stated that it was not a matter in which he had taken any initiative at all.

Health Service Frauds

Mrs. EIRENE WHITE asked the Minister of Health on January 21 if he was satisfied that safeguards against frauds in the Health Service were adequate, in view of the statement by the President of the G.M.C. on undisclosed fraudulent practices.[2] Mr. IAIN MACLEOD replied that the matter was under constant review, but he had no reason to think there was any serious inadequacy.

[1] See *Journal*, November 7, 1953, p. 1038.
[2] See *British Medical Journal Supplement*, December 5, 1953, p. 217.

Mrs. WHITE said that a statement by such a prominent medical authority naturally caused uneasiness. Had the Minister taken any action since it was made? Mr. MACLEOD said that he had not, but it was fair to say that perhaps the right interpretation had not been put on what was said. As he understood it, this was a warning that the G.M.C., quite rightly, took a grave view of any laxity in these matters, and was not an allegation that fraudulent practices or conduct were at all widespread.

Pay-beds in Hospitals

Dr. BARNET STROSS asked the Minister of Health on January 21 whether he was satisfied that pay-beds in hospitals were being fully used, and why, at some hospitals, their use was much less than in the service as a whole. Mr. IAIN MACLEOD said that statistics for last year were not yet available, but he had impressed on hospital authorities the importance of ensuring that the total occupancy of these beds, whether by paying or by non-paying patients, was no lower than that of other beds. Reasons for any unusually low occupancy would depend on the circumstances of the particular case.

Dr. STROSS suggested that the high cost was a factor, and that the whole matter should be reviewed. Would the Minister consider abolishing pay-beds as such, and turning them into normal beds and amenity beds, which would be very much better? Mr. MACLEOD said he certainly would not abolish pay-beds, which he believed had a valuable part, just as had private practice, in the development of the Service.

Welsh Health Statistics

The Minister of Health is arranging for a separate section of the state of the public health in Wales to be included in the next annual report of the Ministry of Health, together with separate statistics of special interest to Wales, according to a Parliamentary answer he gave on January 21.

Calomel in Teething Powders

Mr. S. T. SWINGLER asked on January 21 if the Home Secretary would now prohibit the use of calomel in the manufacture of teething powders. Sir DAVID MAXWELL FYFE replied that he had no power to prohibit the use of calomel in the manufacture of teething powders, but he understood that the only firm known to have been manufacturing such powders wholesale in recent times had decided to omit this ingredient. Retail pharmacists who manufactured their own brands of teething or soothing powders had been advised in the *Pharmaceutical Journal* to use safe aperients in lieu of calomel.[3]

Food and Drugs Bill

When the Food and Drugs Amendment Bill was considered in committee by the House of Lords on January 20 VISCOUNT BLEDISLOE moved a new clause requiring that all milk sold for public consumption must contain at least 3% of butter fat. He said the present policy in regard to the quality of milk sold to the public was fair neither to the public nor to the dairy farmers who tried to produce high-quality milk. What was called the legal presumptive minimum of butter fat content, 3%—which was low compared with requirements in other civilized countries—could be reduced by what was called "an appeal to the cow." He mentioned the practice in several countries where a higher standard was demanded, and said that in Canada and the United States, where 3.5 and even 4% tested milk was not infrequently found, recently the craze for slimming had produced a so-called "slim milk," which was reduced to a 2% content of butter fat; and that a small but significant quantity of skimmed milk was now being sold to those anxious to maintain willowy figures. The "appeal to the cow" was definitely putting a continuing premium on the production of low-quality milk.

LORD SILKIN expressed some doubt that the amendment would result in a shortage of milk. It would mean that there would be a considerable quantity which could not be sold as milk. To improve the quality involved breeding and housing problems that could not be solved immediately. The cost would also be increased.

LORD BALFOUR OF BURLEIGH said that in Kensington sample figures taken over many years showed that the quality of milk sold there was steadily deteriorating. The Government should study the possibility of payment by quality, giving some premium for additional fat content.

LORD WEBB-JOHNSON supported the desire of Viscount Bledisloe to improve the quality of milk, but thought the amendment would lead to a decrease in milk available for consumption, and that would be unfortunate. He agreed with suggestions that the price as well as the milk might be graded. Anything below 3% fat content should be labelled sub-standard milk, but it should be cheaper. For culinary and domestic purposes many people might prefer to buy cheaper milk, leaving available a larger amount of high-grade milk for the infants and children who needed it.

LORD CARRINGTON, Parliamentary Secretary, Ministry of Agriculture, defended the presumptive minimum of 3% and the "appeal to the cow." They were all agreed on the necessity to protect the consumer against deliberate fraud by adulteration of milk, but it would be an entirely new principle to make it a criminal offence to sell a natural product merely because the quality of the product was poor. Farmers had done a magnificent job, and were producing better-quality milk than ever. The proper way to deal with low-quality milk was to see that a lower price was paid for it.

The amendment was withdrawn, after VISCOUNT BLEDISLOE had asked for an assurance that the Government would accept the objective of establishing at no distant date a minimum fat content of 3%, and VISCOUNT WOOLTON had promised to represent this to the appropriate Minister.

Blackburn Maternity Home

Mr. H. HYND asked on January 21 whether the closing of Springfield Maternity Home, Blackburn, was carried out with the Minister of Health's approval, and what consultations took place with the doctors before their patients were ordered to leave the maternity home.[4] Mr. IAIN MACLEOD replied that his approval was not needed, but he was aware of the proposal and saw no reason to dissent. Seven patients were sent home and five transferred elsewhere. Steps were taken to consult all the doctors concerned before action was taken. The doctors of the seven patients accepted the proposal. The doctor of one of the five transferred patients objected. The other four unfortunately could not be reached before transferring, but a message was left for them. He regretted more time was not available for consultation, but understood that no ill effects had followed the transfer.

Mr. HYND indicated that the Minister had been misinformed about whether the doctors were consulted, and asked him to look into the matter again, because of the local indignation about the high-handed way in which the closing took place. Mr. MACLEOD said he would do so. In reply to Mr. R. FORT he said that Springfield, formerly a 20-bed general-practitioner maternity home, was to become a home for 30 chronic sick.

Mrs. BARBARA CASTLE asked whether the Minister was aware that many women were being compelled to have their babies at home owing to the shortage of maternity beds, and that the closing of Springfield would make the situation worse. Mr. MACLEOD replied that even after the Springfield closure the number of general-practitioner beds available was 50%, which was much higher than in most parts of the country.

Mr. HYND gave notice that he would raise the matter on the Adjournment.

[3] See annotation at p. 265.

[4] See *British Medical Journal*, January 23, p. 205.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **January 9** (No. 1) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954 Eng. & Wales	1954 Lond.	1954 Scot.	1954 N. Ire.	1954 Eire	1953 Eng. & Wales	1953 Lond.	1953 Scot.	1953 N. Ire	1953 Eire
Diphtheria	21	1	10	1		22	0	11	0	
Dysentery	322	75	151	1	21	214	12	73	3	
Encephalitis, acute	2	0	0	0		1	0	0	0	
Enteric fever: Typhoid	2	0	0	2		0	0	0	0	2
Paratyphoid ..	1	0	2	0		2	0	0	0	
Food-poisoning ..	141	10		0		72	15		0	
Infective enteritis or diarrhoea under 2 years				9	24				8	15
Measles*	1,134	13	24	24	120	24,738	1905	267	37	164
Meningococcal infection	29	3	19	0		43	2	22	3	1
Ophthalmia neonatorum	32	1	4	0		33	2	10	0	
Pneumonia† ..	994	51	454	11		1,167	90	342	18	1
Poliomyelitis, acute: Paralytic ..	35	4	7	3	4	23	2	0	0	
Non-paralytic ..	9	2				11	1			
Puerperal fever§ ..	212	29	12	1	1	258	33	15	2	1
Scarlet fever ..	792	47	198	31	27	1,238	70	303	23	60
Tuberculosis: Respiratory ..	608	71	113	18				113	22	
Non-respiratory..	92	8	11	4				21	9	
Whooping-cough ..	2,156	83	347	33	62	2,060	121	127	39	135

DEATHS in Great Towns	1954 Eng. & Wales	1954 Lond.	1954 Scot.	1954 N. Ire.	1954 Eire	1953 Eng. & Wales	1953 Lond.	1953 Scot.	1953 N. Ire	1953 Eire
Diphtheria	0	0	0	0	0	0	0		0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute..		0			0		0			0
Enteric fever ..	0	0	0	0		0	0		0	
Infective enteritis or diarrhoea under 2 years	10	2	1	0	3	13	4	5	0	3
Influenza	42	2	4	0	0	51	7	8	0	0
Measles		0	0	0	0		1	1	0	1
Meningococcal infection		1	0				0	2		
Pneumonia ..	385	56	36	10	5	490	87	41	12	17
Poliomyelitis, acute	1	0	1		0	2	0			0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis: Respiratory ..	129	15	20	5	7	127	22	29	7	5
Non-respiratory..		1	1	1	2		3	3	2	3
Whooping-cough ..	1	0	1	0	0	6	2	0	0	0
Deaths 0–1 year ..	270	26	54	11	11	283	39	35	6	21
Deaths (excluding stillbirths) ..	6,811	909	774	123	175	7,617	1216	864	146	236
LIVE BIRTHS .	7,821	1115	1198	256	451	7,683	1153	1081	266	430
STILLBIRTHS ..	201	20	31			201	24	27		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

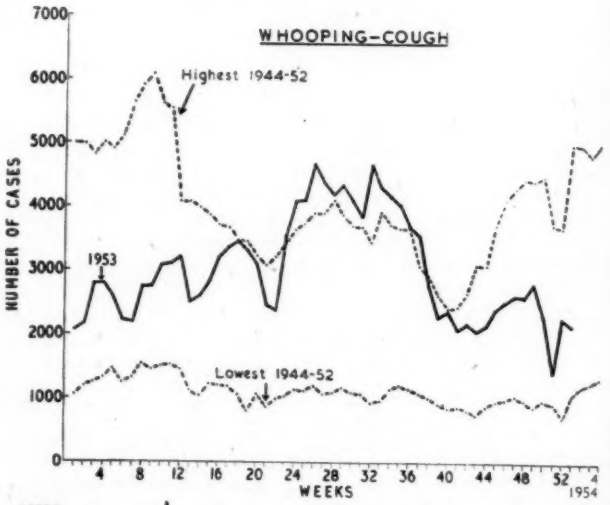
Vital Statistics for 1953

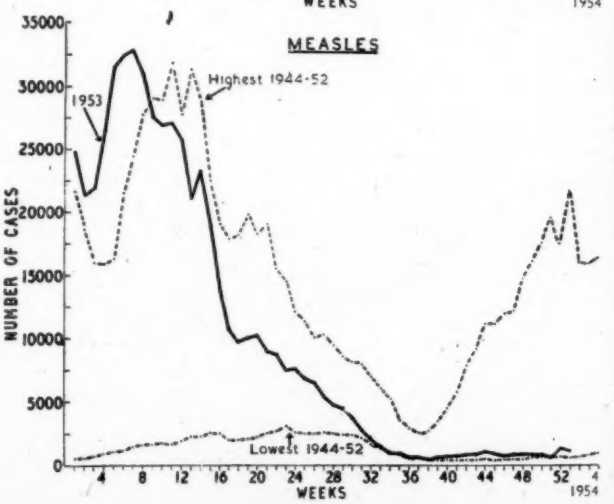
The total of live births registered for the year was 682,007, which was 8,721 higher than the total for 1952, and 2,318 higher than for 1951. The rate per 1,000 population was 15.5, as compared with 15.8, 15.5, and 15.3 respectively in 1950, 1951, and 1952. There were 18,180 deaths of children under 1 year of age, representing a rate of 26.8 per 1,000 related live births, the lowest annual rate ever recorded in this country. This rate compares with 27.6 in 1952 and 52.8 in 1938.

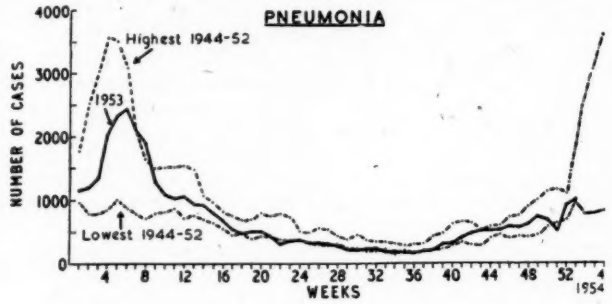
The deaths registered in the year numbered 503,403, giving a rate of 11.4 per 1,000 population, compared with rates of 11.3 in 1952 and 12.5 in 1951. There were 15,630 stillbirths, giving a rate of 22.4 per 1,000 total live and still births. This was a slight improvement on the previous lowest rate of 22.6 in 1952.—*Registrar-General's Weekly Return*, No. 2, 1954.

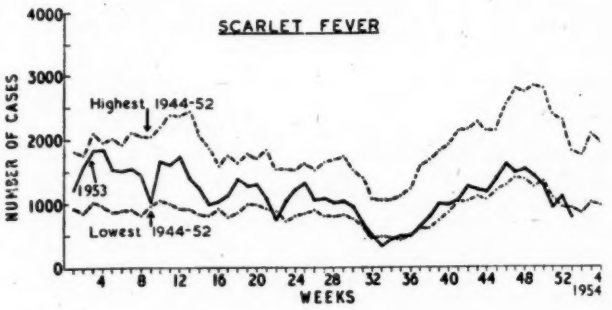
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1944–52 are shown thus - - - - - - - - -, the figures for 1953–4 thus ————. Except for the curves showing notifications in 1953–4, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

Infectious diseases were less prevalent in England and Wales during the week ending January 9. The decreases in the number of notifications included 319 for scarlet fever, from 1,111 to 792; 193 for measles, from 1,327 to 1,134; and 128 for whooping-cough, from 2,284 to 2,156.

A decline in the incidence of scarlet fever occurred in most areas of the country. The largest falls were 67 in Lancashire, from 163 to 96, and 33 in Yorkshire West Riding, from 145 to 112. The largest variations in the returns of measles were an increase of 47 in Lancashire, from 299 to 346, and a decrease of 82 in Staffordshire, from 222 to 140. 21 cases of diphtheria were notified, being 8 fewer than in the preceding week. The chief feature of the returns of diphtheria was a fall in Lancashire from 10 to 2. The largest fluctuations in the trends of whooping-cough were a rise of 43 in Lancashire, from 219 to 262, and falls of 51 in Warwickshire, from 183 to 132, and 35 in Essex, from 142 to 107.

44 cases of acute poliomyelitis were notified during the week. These were 5 fewer for paralytic and 4 fewer for non-paralytic cases than in the preceding week. The largest returns were London 6, Gloucestershire 6 (Bristol C.B. 3), Lancashire 5, and Essex 4.

322 cases of dysentery, 18 fewer than in the previous week, were reported. The chief centres of infection were London 75 (Shoreditch 20, Finsbury 18, Islington 13), Yorkshire West Riding 48 (Leeds C.B. 16, Bradford C.B. 13), Lancashire 37 (Bolton C.B. 18), Essex 20 (Ilford M.B. 13), Norfolk 19 (Norwich C.B. 19), Durham 17, and Leicestershire 17 (Leicester C.B. 17).

Week Ending January 16

The notifications of infectious diseases in England and Wales during the week included scarlet fever 915, whooping-cough 2,366, diphtheria 21, measles 1,150, dysentery 378, acute poliomyelitis 40, paratyphoid fever 4, and typhoid fever 4.

The Services

Brigadier J. Huston, late R.A.M.C., has been appointed Honorary Surgeon to the Queen, in succession to Major-General A. G. Harsant, C.B., O.B.E., late R.A.M.C., who has retired.

Medical News

Cortisone and A.C.T.H. for Blood Disorders.—The Ministry of Health has now added acquired haemolytic anaemia and thrombocytopenic purpura to the list of "obligatory conditions" for which cortisone and A.C.T.H. will be made freely available through special centres at designated hospitals. This step has been taken on the advice of the Medical Research Council, the reports of whose Panel on the Haematological Applications of A.C.T.H. and Cortisone were published in the *Journal* (1952, **1**, 1261; 1953, **2**, 1400). Last August adrenal deficiency, pituitary deficiency, systemic forms of lupus erythematosus, polyarteritis nodosa, pemphigus, exfoliative dermatitis, and sarcoidosis were named by the Ministry as conditions falling into the "obligatory maintenance" category (see *Journal*, August 29, 1953, p. 518).

Interlingua.—In an attempt to break through language barriers, the January issue of *Blood* prints summaries of its original articles in what is described as a "new supranational language," Interlingua, as well as in English. In an editorial Dr. William Dameshek, the editor-in-chief, commends this venture to the readers of *Blood* and to the scientific world at large. Recognizing that "standard average European" is for all practical purposes the language of science, the inventors of Interlingua have gone to Italian, French, English, Spanish, and Portuguese, and have attempted to extract and synthesize all the elements common in them into a logical, readily understandable language. To give an idea of their success, the Interlingua summary of an article on "The Effect of A.C.T.H. in Periodic (Cyclic) Neutropenia" is printed below:

Un caso de neutropenia periodic de un duration de vinti annos es presentate. Administration intravenose de ACTH esseva empleate in le spero de facer abortar o de prevenir le cyclos neutropenic. Nulle effecto in altiar le conto total de leucocytas o neutrophilas esseva constatate, e le cyclos neutropenic non poteva esser prevenite per medio de ACTH. Un frappante absentia de febre, stomatitis, e altere manifestationes secundari esseva notate durante le periodos de therapia a ACTH. Etiam le conditiones governante le tractamento hormonic de tal casos es discutite.

Dr. Dameshek adds that as Interlingua develops words derived from German, Russian, and the various Oriental languages will be incorporated in it.

Travelling Fellowships.—The Medical Research Council invites applications for the following Travelling Fellowships for the academic year 1954–5:

Rockefeller Travelling Fellowships in Medicine.—These Fellowships are provided from a fund with which the Council has been entrusted by the Rockefeller Foundation of New York. They are intended for graduates resident in this country who have had some training in research work in clinical medicine or surgery, or in some other branch of medical science, and who are likely to profit by a period of work at a centre in the United States or elsewhere abroad, before taking up positions for higher teaching or research in the United Kingdom. Fellowships tenable in the United States will normally carry a maintenance allowance at the rate of $2,700 per annum for a single Fellow and $3,600 per annum for a married Fellow. Provision will also be made for travelling and other approved expenses.

Eli Lilly Travelling Fellowships in Medicine.—These Fellowships, tenable in the United States, will be provided from a special fund placed at the disposal of the Council by Eli Lilly and Company, U.S.A. Four Fellowships will be available for the academic year 1954–5, and the awards will in general be made on terms and conditions similar to those attaching to the Rockefeller Travelling Fellowships in Medicine.

Dorothy Temple Cross Research Fellowships in Tuberculosis.—These Fellowships are awarded by the Council from a special endowment of which it is the trustee. The

object of the Fellowships, as defined in the Trust Deed, is to give special opportunities for study or research to suitably qualified British subjects of either sex "intending to devote themselves to the advancement by teaching or research of curative or preventive treatment of tuberculosis in all or any of its forms." The Fellowships will, as a rule, be awarded to candidates who wish to make their studies or inquiries elsewhere than in the United Kingdom. The Fellowships provide for the payment of a maintenance allowance at the rate of £650 per annum for a single Fellow and £900 per annum for a married Fellow, subject to appropriate adjustment in the case of Fellowships tenable at centres outside the sterling area; in addition, an allowance will be made for travelling and other approved expenses.

Further particulars and forms of application may be obtained from the Secretary, Medical Research Council, 38, Old Queen Street, Westminster, S.W.1, with whom applications must be lodged not later than March 15, 1954.

Medical Auxiliaries.—It is nearly a year since the Minister of Health, answering a Parliamentary question about the Cope report, stated that he would make regulations laying down the qualifications required of medical auxiliaries employed in the National Health Service. The National Health Service (Medical Auxiliaries) Regulations, 1954, have now been issued, and after April 1, 1954, hospitals and local health authorities may employ only those qualified under them. The regulations refer to two groups of auxiliaries—those who on March 31, 1954, come within the definition of being qualified on that date, and those who will qualify on or after April 1. The first group comprises (1) those who are already employed in the N.H.S.; (2) those who hold qualifications recommended by the Cope Committee as appropriate; and (3) certain holders of qualifications given by the Joint Council of Chiropodists and the Physiotherapists Association. Those qualifying after April 1 must obtain a certificate from one of the appropriate bodies named in the regulations. Employing authorities can accept the certificates when the Minister has approved the course of training and examinations to which the certificate refers. The Cope Committee recommended that there should be statutory registration for medical auxiliaries. The Minister said in Parliament that there was insufficient agreement on fundamental matters to proceed with this—an opinion with which we disagreed (June 6, 1953, p. 1267). The Minister has now announced that he is setting up a Working Party to draw up a scheme of registration which will be acceptable to him and to the professional bodies concerned.

Rockefeller Grants.—Among the Rockefeller grants announced this quarter perhaps the two of most interest to medical men are those to Professor Vincent du Vigneaud, of Cornell University, for the continuation of his work on what appears to be synthetic oxytocin (see *Journal*, December 5, 1953, p. 1260), and to the School of Public Health, Harvard, the Christian Medical College of Ludhiana, Punjab, and the Government of India for a pilot study in the Punjab preparatory to a long-term investigation of "population dynamics" in India. Individual British workers who are awarded grants include: Professor J. M. Yoffey at Bristol for research in experimental histology and physiology ($6,200); Dr. Max Perutz, director of the M.R.C. Unit for Research on the Molecular Structure of Biological Systems at Cambridge, for equipment ($4,000); Dr. H. Lehmann, to visit centres of sicklaemia research in the United States ($2,505); Dr. Robert Murray, a medical inspector of factories in Lancashire, for a visit to occupational health and hygiene centres in the United States and Canada ($2,350); Professor A. V. Hill for visits to the scientific conferences and centres of biophysical research in the United States ($2,100); and to Oxford University for equipment to be used in the Subdepartment of Microbiology under Dr. D. D. Woods.

President's Tour.—Sir Cecil Wakeley, P.R.C.S., has just returned from a two months' visit to Ceylon and the Middle East. He went to open the ninth annual session of the Ceylon Society for the Advancement of Science, where he spoke on "Surgery through the Ages." While in Ceylon, he gave a broadcast on "Positive Health" and a B.M.A. lecture on the surgery of the temporo-mandibular joint, as well as lectures to the Medical Society of Kandy and the Dental Society. On his return journey, at the invitation of General Sir Charles Keightley, Sir Cecil spent a day inspecting the Army medical services in the Canal Zone. He saw a demonstration of the Fleming mass inoculation technique, which is rapidly becoming the standard method there, and a hospital surgical service where the regimental medical officer brings his patients for minor surgery instead of doing it in the unit medical inspection room. In the afternoon there was a joint clinical meeting of the medical services of the Royal Navy, Army, and R.A.F. at the British Military Hospital, Fayid, under the chairmanship of Major-General W. A. D. Drummond.

The Common Cold.—Aptly situated on one of the bleakest hilltops in England, the Common Cold Research Unit at Harvard Hospital, just outside Salisbury, opened its doors to the Press on January 21. This hospitality is rarely possible, because the claims of complete isolation must normally come first. Dr. C. H. Andrewes, F.R.S., director of the studies there, outlined the work that had been carried on for the last six years. Some advance has been made towards the control of this exceedingly obdurate virus in that, as reported last year, it is being serially propagated in fragments of human embryonic lung, but human volunteers are still needed to detect its presence. It has been found that the most active nasal washings produce colds in only 55% of women and 43% of men aged 18–40, and a possibly fruitful line for further research is thought to be a study of why individuals differ in their susceptibility.

North of England Obstetrical and Gynaecological Society.—At the annual general meeting of the North of England Obstetrical and Gynaecological Society, held in Manchester on January 15, honorary fellowship was conferred on Sir William Fletcher Shaw (Manchester), Dr. Henry Brown (Brighton), and Dr. W. A. MacKay (Southport), all of whom have been members of the society for over 45 years. The following officers were elected for 1954: *President*, Dr. K. V. Bailey; *Hon. Treasurer*, Dr. C. H. Walsh; *Hon. General Secretary*, Mr. D. C. Racker; *Hon. Reporting Secretary*, Mr. S. Bender.

COMING EVENTS

Society for Endocrinology.—The next meeting will be held jointly with the Endocrinological Section of the Royal Society of Medicine at 1, Wimpole Street, London, W.1, on February 24 at 10 a.m. It will take the form of a symposium on "The Technique and Significance of Oestrogen Determinations." Those wishing to attend who are not members of either society should write to Professor N. F. Maclagan, Westminster Medical School, 17, Horseferry Road, London, S.W.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ● Applications should be made first to the institution concerned.

Monday, February 1

INSTITUTE OF DERMATOLOGY.—Fifth of series of semi-permanent exhibitions by Mr. R. J. Lunnon: Medical Photography. (February 1 to 20.)

Tuesday, February 2

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor L. P. Garrod: Causes of Failure in Antibiotic Therapy.

LIVERPOOL MEDICAL INSTITUTION.—At Newsham General Hospital, Liverpool, 3 p.m. clinical meeting.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Mr. J. R. Armstrong and Mr. Aleck W. Bourne: Backache in Women.

Wednesday, February 3

EDINBURGH CLINICAL CLUB.—At the City Infectious Diseases Hospital, Edinburgh, 4 p.m., clinical meeting. Dr. G. Sangster: Gastro-enteritis in Infants.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Practical Diagnosis of Superficial Mycoses.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Professor P. Van de Calseyde (Bruges): Bronchial Diseases and Pathology of the Upper Respiratory Tract, Clinical Aspects and Therapeutic Conclusions.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Dr. J. J. Stevenson: *X*-rays.

●LONDON UNIVERSITY: DEPARTMENT OF EXTRAMURAL STUDIES AND ATOMIC SCIENTISTS' ASSOCIATION.—At Beveridge Hall, Senate House, 7 p.m., Professor F. E. Simon, F.R.S.: Power from Atomic Energy.

MANCHESTER MEDICAL SOCIETY: SECTION OF MEDICINE.—At Large Anatomy Theatre, Manchester University, 4.30 p.m., Dr. W. H. Trethowan: Psychopathological Reactions to A.C.T.H. and Cortisone.
MIDLAND MEDICAL SOCIETY.—At Birmingham Medical Institute, 8.15 p.m., Dr. T. L. Hardy: Functional Disorders of the Colon.

Thursday, February 4

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor A. A. Miles: Reactions to Bacterial Invasion.
FACULTY OF HOMOEOPATHY.—5 p.m., Drs. W. Lees Templeton, L. R. Twentyman, E. K. Ledermann, C. O. Kennedy, and N. J. Pratt: Reports on Research.
●INSTITUTE OF CHILD HEALTH.—5.30 p.m., Mrs. J. M. Williams: Prevention of Backwardness at School.
LONDON UNIVERSITY.—(1) At School of Pharmacy, 5.30 p.m., Special University Lecture in Pharmacy by Professor J. H. Gaddum, F.R.S.: Discoveries in Pharmacology. (2) At Senate House, 5.30 p.m., Special University Lecture by Air Marshal Sir Harold Whittingham: Medical Science and Problems of Flying.
MANCHESTER MEDICAL SOCIETY: SECTION OF ANAESTHETICS.—At Medical School, Manchester University, 8 p.m., Dr. E. A. Pask: James Brown.
OXFORD UNIVERSITY.—At Southfield School, Glanville Road, Cowley Road, Oxford, 8 p.m., Dr. A. G. M. Weddell: Science and Medicine.
ROYAL COLLEGE OF SURGEONS OF ENGLAND AND INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—At Royal College of Surgeons of England, 5.30 p.m., Professor G. Hadfield: Co-carcinogenesis.
ST. ANDREWS UNIVERSITY.—At Physiology Department, Dundee, 5 p.m., Dr. J. N. Morris: Epidemiological Approaches to Coronary Disease.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., psychiatry demonstration by Sir Paul Mallinson.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, 5.30 p.m., Public Lecture by Professor F. Bergel, Ph.D., D.Sc.: Some Chemical Aspects of Abnormal Growth.

Friday, February 5

INSTITUTE OF CARDIOLOGY.—9.30 a.m., Dr. S. J. Sarnoff (Harvard): Haemodynamic Effects of a New Sympathomimetic Amine, Aramine, and the Rationale for its Use in the Hypotension and Low Cardiac Output of Myocardial Infarction.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. H. W. Gordon: Benign New Growths.
INSTITUTE OF NEUROLOGY.—5 p.m., Professor H. Gastaut (Marseilles): So-called "Psychomotor" and "Temporal" Epilepsy.
LONDON UNIVERSITY.—At School of Pharmacy, 5.30 p.m., special university lecture in pharmacy by Professor J. H. Gaddum, F.R.S.: Discoveries in Pharmacology.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Mr. J. E. Richardson: Unusual Presentation of Common Gastric Disorders.
ROYAL MEDICAL SOCIETY, Edinburgh.—8 p.m., Dissertation by Mr. D. Q. Sutherland: Mind over Matter.
WHIPPS CROSS HOSPITAL MEDICAL SOCIETY.—8.30 p.m., Dr. Hugh Ramsay: Tuberculosis Services, Yesterday and To-day.

Saturday, February 6

KENT PAEDIATRIC SOCIETY.—At Royal Star Hotel, Maidstone, 2.15 p.m., discussion by Mr. R. H. Percival and Dr. P. N. Swift: Circumcision.
MIDLAND TUBERCULOSIS SOCIETY.—At Birmingham Chest Clinic, Mr. P. R. Allison: Some Diseases at the Lower End of the Oesophagus.

APPOINTMENTS

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—G. L. Davies, M.R.C.S., L.R.C.P., D.P.M., Assistant Psychiatrist, Ipswich Child Psychiatry Clinic; W. Boyd, M.B., Ch.B., Senior Registrar in Mental Deficiency and Child Psychiatry, Little Plumstead Hospital; W. P. D. Green, M.B., B.S., Senior Medical Registrar, East Suffolk and Ipswich Hospital; K. W. Baruch, M.B., Ch.B., Anaesthetic Registrar, West Suffolk General Hospital; J. A. Reynolds, M.R.C.S., L.R.C.P. and T. K. Thorlakson, M.D., F.R.C.S., Surgical Registrars, East Suffolk and Ipswich Hospital; E. A. Burkitt, M.R.C.S., L.R.C.P., D.P.M., Assistant Psychiatrist, Hellesdon Hospital, Norwich.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Arndt.—On January 15, 1954, at Queen Charlotte's Hospital, London, W., to Frances (formerly Ondatje), M.B., B.S., D.Obst.R.C.O.G., wife of Reverend George Arndt, a daughter—Theonie Frances.
Gibb.—On January 3, 1954, at St. Bartholomew's Hospital, London, E.C., to Mary (formerly Feetham), wife of William Eric Gibb, D.M., F.R.C.P., a son.
Griffiths.—On December 18, 1953, at King's College Hospital, London, S.E., to Barbara (formerly Grand), wife of Dr. Glyn I. T. Griffiths, a second daughter—Caroline Barbara.
Levis.—On December 31, 1953, at the Central Middlesex Hospital, London, N.W., to Renée (formerly Anderson), wife of R. D. Levis, M.B., D.A., a daughter—Julia Alison.
Rutherfoord.—On January 19, 1954, at 192, Staines Road, Bedfont, Middlesex, to Tess (formerly Tomlinson), wife of Dr. G. T. Rutherfoord, a son.
Williams.—On December 21, 1953, in Nairobi, Kenya, to Philippa Gaffikin, M.B., Ch.B., wife of John G. Williams, a daughter.

DEATHS

Clarke.—On January 9, 1954, at 74, Earlham Green Lane, Norwich, Norfolk, Andrew Campbell Clarke, M.B.E., M.D., aged 79.
Corcoran.—On January 1, 1954, at 48, Queen's Gate, London, S.W., Gerald Corcoran, L.R.C.P.&S.I.&L.M., D.P.H., formerly of Southsea, Hants.
Crerar.—On January 7, 1954, at The Whin, Snape, Suffolk, John William Crerar, M.B., F.R.C.S.Ed., of Maryport, Cumberland, aged 86.
Davies.—On January 2, 1954, at 113, Fox Lane, Palmer's Green, London, N., Sidney Richard Eccles Davies, M.R.C.S., L.R.C.P., D.P.H.
Lloyd.—On December 22, 1953, at 4, Overdale, Ashtead, Surrey, Richard Harte Lloyd, M.R.C.S., L.R.C.P., Colonel, late R.A.M.C., retired.
Rentzsch.—On December 27, 1953, at St. Lawrence's Hospital, Bodmin, Cornwall, Sigismund Henry Rentzsch, M.R.C.S., L.R.C.P., aged 87.
Roberts.—On January 1, 1954, at his home, Garth, Fairfield Avenue, Rhyl, Flints, Aneurin Evan Roberts, M.B., B.S., D.P.H.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Mouth-breathing

Q.—*Is there any effective treatment for re-establishing nose-breathing in children who have had tonsils and adenoids removed and in whom there is no nasal obstruction? Is diastolization still used for this?*

A.—Defective nose-breathing in a child may be due to a cause within the nasal cavity itself, to excessive lymphoid tissue in the post-nasal space (adenoids), or to habit.

It is customary to attribute any nasal symptoms in a child to adenoids, just as it is usual to attribute such symptoms in an adult to "catarrh." In both cases a proper examination of the nose after a careful history has been taken should be the rule. In not a few instances it will be found that the nasal obstruction is variable, possibly being worse in the morning on rising, and then an allergic cause should be considered. If the possibility of allergy has been excluded, and enlarged tonsils and adenoids have been removed, and the nasal airway seems clear, then the possibility of habit must be considered. Children who have of necessity been habitual mouth-breathers acquire a pattern of mouth-breathing which is continued even when the nasal airway has been restored. For these, breathing exercises are needed.

In some there may be a dental malformation which requires correction, and in very persistent mouth-breathers who have a good nasal airway it may be necessary to prescribe an obturator for wearing at night.

Diastolization is not generally practised now, though at one time it was popular in some children's clinics.

Anticoagulant Therapy at Sea

Q.—*I sometimes have to treat cases of coronary occlusion while at sea, where no elaborate laboratory facilities are available. Should anticoagulants be used in these circumstances? If so, which are advised, how should they be given, and what is the minimum essential laboratory control?*

A.—None of the anticoagulants which act by depressing the liver function should be used without laboratory facilities for measuring the prothrombin time from day to day: this applies to dicoumarol, ethyl biscoumacetate ("tromexan"), and "dindevan." Heparin, however, may be used safely without laboratory tests, and may be given in doses of 12,500 units twice daily, intramuscularly or intravenously. Intramuscular heparin is usually painful, and is best combined with 1 ml. of 2% procaine. Heparin is supplied in ampoules of 25,000 units per ml., or in a weak strength of 5,000 units per ml. The injections should be given with the least trauma possible; severe bruising at the site of the injection occurs sometimes despite precautions, but it is very rarely serious. At sea, the clotting time could easily enough be measured if there was any doubt about dosage, but the test would vary considerably according to the time it was done after the injection. One should aim at keeping the clotting time between two and three times normal. Protamine sulphate should be available so that the heparin could at once be neutralized if spontaneous haemorrhage occurred. It should be given intravenously in a dose of about 100 mg., repeated if necessary. One milligram of protamine neutralizes approximately 1 mg. of heparin. Anticoagulant treatment, if used at all, should be continued for three weeks at a minimum.

Travellers' Diarrhoea

Q.—*Does the intestinal flora change when a person moves from one locality to another, and is this the cause of the attacks of enteritis which quite often accompany a change of habitat? What can be done to prevent them?*

A.—Little is known about the normal composition of the intestinal flora, and no studies have been made of changes, if any, which follow movement of an individual from one locality to another. It has been conjectured that such changes might form the basis of the attacks of diarrhoea which commonly affect new arrivals in various districts, but of this there is no proof. The recent discovery that in children certain coliform organisms may cause enteritis opens up the possibility that diarrhoea in adults may be caused by similar organisms.

To make special efforts to maintain a high standard of hygiene while moving from one locality to another is the best method of preventing these attacks of enteritis. When travelling in the Tropics or setting up house in a new station, food and drink are often obtained, or may only be obtainable, from dubious sources. In these circumstances bacterial infections are readily acquired, as it may be difficult to boil drinking water or to ensure that salads and other uncooked foods are adequately prepared. To avoid such articles of diet and unboiled drinking water is probably the most important single hygienic measure in the prevention of the attacks of enteritis.

Burial of the Dead

Q.—*What is the law on the burial of the dead? In particular, what regulations must be complied with before burial? Must the fact of burial be notified? May burial be elsewhere than in a churchyard? May it be an entirely secular affair? May burial be performed after dark?*

A.—The law on burial of the dead cannot satisfactorily be compressed into a brief statement. It is embodied in a number of statutes, enacted between 1853 and 1906. Repeal or amendment of several of their provisions has created a situation which calls for the reconsideration of the whole field and consolidation of the law in a new statute. Reference should be made, in particular, to *The Law of Burial* (Fellows, A., 2nd edition, Hadden, Best & Co., London, 1952) and to *The Disposal of the Dead* (Polson, C. J., Brittain, R. P., and Marshall, T. K., English Universities Press, London, 1953).

The regulations which apply to burial will depend upon the circumstances. When the death is due to natural causes, and is not a matter for report to the coroner, the first step is the issue of a medical certificate of cause of death and a notice to the informant by the registered medical practitioner who was in attendance upon the deceased during his or her last illness. These documents are required by the registrar of births and deaths before he may register the death, which step, in normal circumstances, must also be taken before burial is lawful. In addition, the person effecting disposal of the remains must notify the registrar within 96 hours of so doing. Burial after an inquest, or after a post-mortem examination ordered by the coroner but without the holding of an inquest, calls for modified procedure. It is also possible to effect burial prior to registration of the death provided written notice, supported by a medical certificate of cause of death, is received by the registrar. In these circumstances the informant is required to attend at the office of the registrar in order to complete the process of registration of the death.

Burial may take place not only in a churchyard but also in a burial ground, cemetery, or, for that matter, in any place conforming with regulations that relate to public health and town and country planning. Burial at sea is also lawful.

Burial may be an entirely secular affair. The Burial Laws Amendment Act, 1880, provides that burials may take place in the churchyard or burial ground of any burial board, without the service of the Anglican Church (section 1); and the burial can take place without any kind of religious service if the person in charge of the burial so desires (section 6).

Burial may take place after dark, but it is advisable to consult the authorities in charge of the proposed place of burial, since their by-laws will probably include special provisions which concern unusual times of burial.

Streptomycin in Pregnancy

Q.—*I would be grateful for an answer to the following query on the antibiotic treatment of pulmonary tuberculosis during pregnancy. It has been suggested that streptomycin reaches a high concentration in the amniotic fluid and causes damage to the vestibular apparatus of the foetus. Is this correct?*

A.—Streptomycin has now been given to many pregnant women. There is no evidence that it has ever caused damage to the vestibular apparatus of the foetus. Streptomycin should not therefore be withheld from pregnant women who need it.

Ascorbic Acid and Phenylbutazone

Q.—*I have gained the clinical impression that the administration of 50 mg. ascorbic acid with phenylbutazone increases the effectiveness of the latter drug. Is this effect recognized, and, if so, what is its mechanism?*

A.—There is no scientific basis for believing that ascorbic acid increases the effectiveness of any analgesic drug, although "clinical impressions" to this effect have been recorded not infrequently. There is no contraindication to such a combination being given if this belief is held.

NOTES AND COMMENTS

Ergot Preparations and Migraine.—Dr. J. N. G. DRURY (Blaby) writes: In your expert's reply to a query about ergot preparations and migraine ("Any Questions?" November 28, 1953, p. 1230) he says that dihydroergotamine may be used prophylactically, but the results are capricious, and its major value is when given at the first warning of an attack. I started to use this preparation two years ago and have had a small series of cases—ten or so—under observation for most of the time. No males have been treated. The frequency of onset of headache has been from two headaches a week to one a fortnight. All patients stated they had been nearly "laid out" by the headaches, and occasionally had to go to bed. I beg humbly to differ with your expert in that I believe the use of dihydroergotamine prophylactically is of more value (almost) than when given for an attack. All my patients have been taking five drops or so daily with 30 drops at the onset of an attack. I can say that in all cases the interval has been lengthened considerably—possibly one per month—and the "knock-out" attack now occurs infrequently. I have not observed any untoward side-effects. The patients complain only if for any reason they have not kept up taking the drops and the headache returns.

OUR EXPERT writes: This is an interesting series and further observations would be useful. Certainly dihydroergotamine is not always a successful prophylactic.

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